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## Original Communications

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### STUDIES ON THE NUCLEATED RED CELL COUNT IN THE CHORIONIC CAPILLARIES AND THE CORD BLOOD OF VARIOUS AGES OF PREGNANCY

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EVER since the presence of nucleated red cells in the peripheric blood of the newborn infant became known, their significance has been a matter of dispute. In recent years there has been pronounced resumption of this debate. The studies of erythroblastosis naturally have turned to the blood picture in the newborn infant in an attempt to define variations of the normal count.

#### REVIEW OF LITERATURE

The first investigations as to the presence of nucleated red cells in the blood of the newborn infant are accredited to Neumann<sup>1</sup> in 1871. Lippman,<sup>2</sup> in his study of the newborn blood, listed the observations of several investigators, on the number of nucleated erythrocytes, which we have included in Table I. According to Lippman, Fischel<sup>3</sup> was not impressed by the number of erythroblasts in the normal full-term newborn infant, but he had noticed their presence in premature infants. Loos,<sup>4</sup> Geissler and Japha,<sup>5</sup> in 1895, concluded that normoblasts did not occur in the blood of the normal newborn infant, and that their presence, therefore, must be considered as a pathologic sign. According to Heimann,<sup>6</sup> erythroblasts were not common in icterus neonatorum. Karnitzki<sup>7</sup> found nucleated erythrocytes in the blood of an otherwise normal nursing seven and one-half months of age. In recent years observations were directed to the study of nucleated red cells in erythroblastosis. Buchan and Comrie<sup>8</sup> first noted in 1909 that widespread hemopoiesis is the underlying pathologic condition in icterus gravis. Rautmann<sup>9</sup> and Schridde<sup>10</sup> investigated

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

TABLE I. CHRONOLOGIC DATA OF VARIOUS AUTHORS ON NUCLEATED RED BLOOD CELLS

AUTHOR	YEAR	OBSERVATIONS
Neumann, E. <sup>1</sup>	1871	First observer to see nucleated red blood cells in newborn blood.
Vierordt, K. <sup>25</sup>	1872	Confirmed Neumann's observations.
Elder and Hutchinson <sup>26</sup>	1895	Found an average of 5 to 12 erythroblasts per 100 leucocytes.
Carstanjen, M. <sup>27</sup>	1900	Found an average of 1.3 nucleated red blood cells per 100 leucocytes.
Aiken, J. <sup>28</sup>	1902	Found erythroblasts in all cases directly after birth: at 48 hours after birth in 24 out of 25 cases; at 5 to 9 days, 15 out of 27 cases.
Fehrson, A. O. <sup>29</sup>	1903	Always found erythroblasts present in first two hours after birth; never after thirteen hours.
Takasu, K. <sup>30</sup>	1904	Found nucleated red blood cells in all cases.
Grawitz, E. <sup>31</sup>	1906	Found nucleated red blood cells in 3 of 15 infants.
Biffi and Galli <sup>32</sup>	1908	Observed nucleated red blood cells in 28 of 29 cases.
König, H. <sup>33</sup>	1910	Found nucleated red blood cells in 92 per cent of cases.
Slawik, E. <sup>34</sup>	1920	Found average of 6 nucleated red blood cells per 100 leucocytes present in 14 of 25 cases in second week.
Lucas, W. P., et al. <sup>35</sup>	1921	Found nucleated red blood cells in 52 per cent of cases on first day, with average of 1 per 100 leucocytes; 5 per cent of cases on second day, with average of $\frac{1}{2}$ a nucleated red blood cell per 100 leucocytes.
Lippman, H. S. <sup>2</sup>	1924	Studied 71 infants: greatest number of nucleated red blood cells at birth, with sudden decrease until fifth day when only 1 cell seen in 30 cases. Highest count 37.8 per cent.
Heath, E. <sup>36</sup>	1926	Found minimum value of 0.3 per cent and maximum of 31.3 per cent. Suggested possibility of pathologic conditions with high counts.
Büngeler and Schwartz <sup>12</sup>	1927	Found 1-1.5 nucleated red cells per 100 leucocytes, with highest value 24 per 100 leucocytes. Postulated "birth crisis."
Forkner, C. E. <sup>37</sup>	1929	38.5 per cent of cases had nucleated red blood cells on first day of life.
Javert, C. T. <sup>13</sup>	1939	Found average of 10 nucleated red blood cells per 100 leucocytes.

the pathologic basis of universal edema of the newborn infant. The term "erythroblastosis" was introduced by Rautmann.<sup>9</sup> Kleinschmidt<sup>11</sup> found the blood picture in a case of icterus neonatorum resembled that of an embryo between three and five months of age. We have listed in Table II abnormal values of blood smears in the newborn blood according to various authors. Here we shall call attention to the paper of Büngeler and Schwartz<sup>12</sup> which, unfortunately, did not receive any comment in the literature of recent date. Büngeler and Schwartz,<sup>12</sup> in 1929, did not find any basic differences in the blood pictures which could be correlated directly with the birth weight of premature infants, although the highest number of normoblasts was found in premature infants with very low weights. They also noticed the rapid disappearance of nucleated red blood cells on the second, third, or fourth day of life. This fact has been stressed by Javert.<sup>13</sup> They felt that the nucleated cell count could be used as an indicator of the viability of the newborn infant. According to Büngeler and Schwartz,<sup>12</sup> normoblasts in the blood of the newborn full-term infant are not a physiologic phenomenon in the strict sense but rather conditioned

TABLE II. ABNORMAL VALUES OF NUCLEATED RED BLOOD CELLS  
Review of Several Authors

AUTHOR	YEAR	NUCLEATED RED CELLS PER 100 LEUCOCYTES	DISEASE
Schridde, H. <sup>10</sup>	1910	53 nucleated red blood cells per 100 leucocytes	Congenital hydrops
Salomonsen, L. <sup>38</sup>	1931	49 nucleated red blood cells per 100 leucocytes	Congenital hydrops
Shapiro and Cohen <sup>39</sup>	1939	Found values of 369 and 364 nucleated red blood cells per 100 leucocytes	Congenital hydrops
Javert, C. T. <sup>13</sup>	1939	a. Found values of 362, 110, and 1,324 nucleated red blood cells per 100 leucocytes.	Erythroblastosis fetalis
		b. Values of 44 to 52 and 70 nucleated red blood cells per 100 leucocytes.	Congenital abnormalities
		c. Values varying from 20 to 84 nucleated red blood cells per 100 leucocytes.	Prematurity
Wolf and Neigus <sup>40</sup>	1940	a. Found variations from 21, 16, 41, 58, 143, 85 to 300 nucleated red blood cells per 100 leucocytes.	Icterus gravis
		b. Values of 78 and 149 per 100 leucocytes.	Erythroblastosis

by an abnormal act of delivery. Büngeler and Schwartz<sup>12</sup> also noted immature white cells parallel to an increase of nucleated red cells in the first days of life. Conversely, in the absence of immature white cells, nucleated red cells were not present or only in very small numbers. These authors interpreted these cells as signs of, or reactive phenomena to, tissue damage, especially hemorrhages, during the act of delivery. Disintegration of tissue and blood, which is avidly resorbed in this early period of life, leads to a noticeable increase of white cells and, especially, to the liberation of nucleated red blood cells. Injection of embryonic juice into rabbits produced an analogous increase in the number of immature white and nucleated red blood cells. These abnormal cells disappeared from within twenty-four to forty-eight hours. Their elaborate study led them to postulate a "birth crisis" in the blood picture of the newborn infant which they feel is conditioned by tissue damages during the course of delivery. Some data published by these authors seemed of particular significance. In many cases the blood pictures were absolutely identical with those of a normal adult, in spite of the decidedly premature state of the newborn infant. On the other hand, in full-term infants (determined by the usual standards of weight, length, and duration of pregnancy), a considerable increase of immature red and white cells was seen; especially in children born after prolonged labor or after considerable damage to the cranium or other organ systems, as proved by post-mortem examinations.

Among more recent observations, we wish to call attention to those of C. T. Javert<sup>13</sup> who believes that routine cord blood smears can be used as a more accurate criterion of prematurity and maturity than the standards so far accepted. This statement certainly cannot be reconciled with the studies of Büngeler and Schwartz.<sup>12</sup> According to Javert,<sup>13</sup> a certain number of nucleated red cells (10 or more) per 100 white cells, is in itself a sign of prematurity, regardless of whether or not weight, length, and duration of pregnancy are also pointing to prematurity. That high nucleated red cell counts might be caused by asphyctic conditions, as for example, in congenital heart disease, is pointed out in the paper by Hellman and

Hertig.<sup>14</sup> They found such an increase of nucleated red cells which, in examining the chorionic capillaries, might be confused with erythroblastosis. Javert,<sup>13</sup> too, has noted that in the blood smears from cases with different abnormalities and from asphyxiated babies, in general, an increased number of nucleated erythrocytes was found.

It is the purpose of this paper to add more material to this question, dealing with the number of nucleated red cells in the newborn infant, which is still unsettled, as we believe. Correlation of post-mortem findings to the blood picture seen in the cord smears seems of distinct value, especially with regard to some of the views expressed in the recent literature. At the same time we also wish to add in the frame of this study more material of simple diagnostic value in the very early phases of pregnancy, as revealed in routine examinations of curettings from abortions. Ever since 1930 this histologic procedure, introduced by K. Terplan, has proved its reliability in determining the age of pregnancy, especially in the first twelve weeks. Ryerson and Sanes<sup>15</sup> have summarized the entire material examined in the Pathological Laboratory of the Buffalo General Hospital until the year 1934. While in our routine histologic procedures the number of nucleated red cells in chorionic capillaries was more or less roughly estimated, Ryerson and Sanes<sup>15</sup> actually enumerated the nucleated red cells and determined their ratio to the nonnucleated red cells in the chorionic capillaries. With this ratio the age of the pregnancy within the early phases could be determined fairly accurately, and these estimates in many cases could be controlled by reliable clinical data and the length of the embryo. The figures reported by Ryerson and Sanes<sup>15</sup> were confirmed by Ohringer,<sup>16</sup> in Germany, and by Halpert and Stasney,<sup>17</sup> in this country. Ryerson and Sanes<sup>15</sup> mentioned the possibility that counting of nucleated red cells in the chorionic capillaries might be used to detect fetal erythroblastosis in more mature pregnancies.

We wish to show that examination of the nucleated red blood cells in the chorionic capillaries reveals rather constant figures for the normal newborn infant. Whenever these values are altered, certain conclusions may be drawn.

#### MATERIAL EXAMINED

Two hundred and sixty placentas were received, as a rule immediately following delivery. These included full-term and premature births and also some late abortions. There were 200 placentas at full term. They were weighed, diameters measured, carefully inspected, and any findings of infarcts, length, and insertion of cord recorded. Sections in vertical and horizontal (parallel) planes were taken and for forty-eight hours fixed in Orth's fluid (this mixture was given preference because of its excellent fixation of the red blood cells). They were embedded in paraffin in the usual way. Sections were cut at 8 microns and stained with hematoxylin-eosin. One thousand red blood cells were counted within the lumina of the chorionic capillaries with the oil immersion lens. The ratio of the nucleated to nonnucleated erythrocytes, as found in the placentas, is given in Fig. 1.

In addition to this enumeration of red blood cells in the chorionic capillaries, blood was aspirated from the umbilical cord of full-term and premature infants, including also all those cases of abortions in which blood could be obtained. The smears were

stained according to Wright's method. The usual differential count of 100 leucocytes was done, and as nucleated red blood cells (normoblasts, erythroblasts, proerythroblasts) appeared, they were counted separately. That number, therefore, is related to 100 white cells. Our findings are recorded in Fig. 2.

In many instances of fetuses under 2,500 Gm., we were unable to correlate the cord blood smear with the findings in the chorionic capillaries. In some of these, we had received only the placenta, and cord blood smears were not obtainable. In addition, we were fortunate to have the opportunity to study cord blood smears from 4 cases of erythroblastosis and the placenta in one of these.

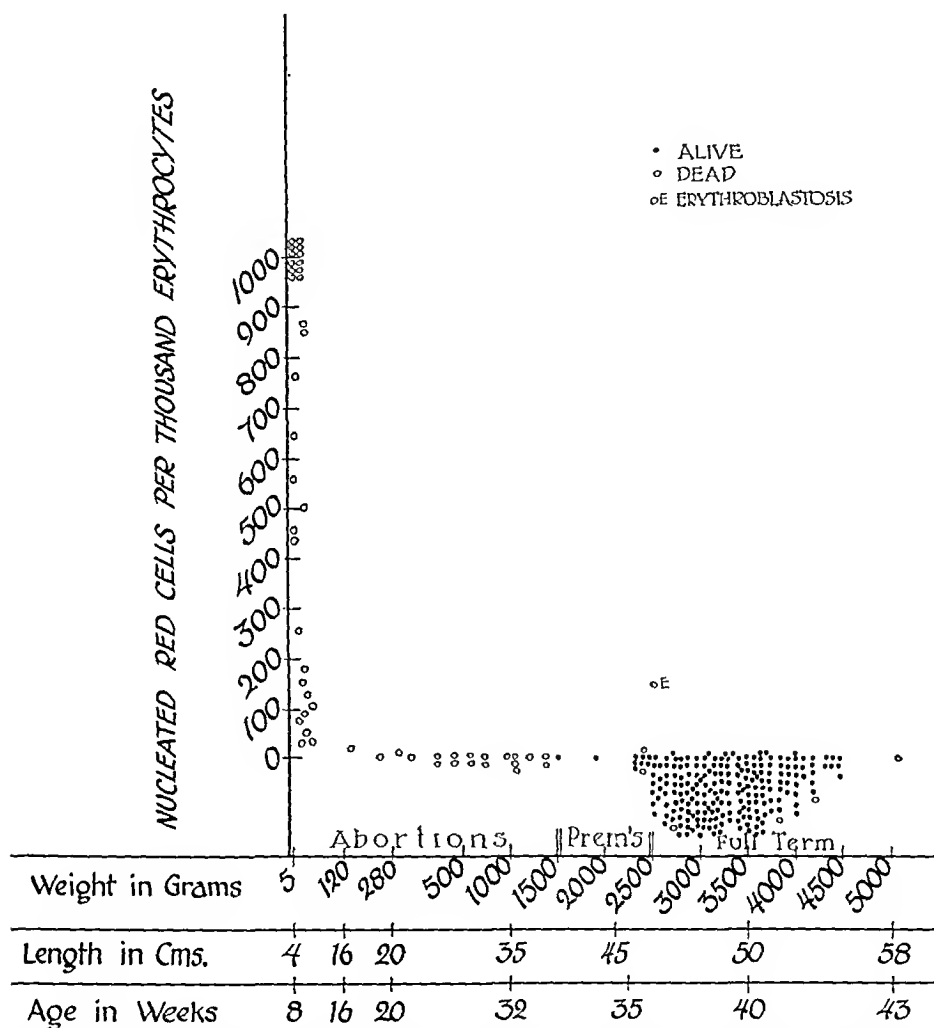


Fig. 1.—Scattergram, showing nucleated red cell counts per one thousand erythrocytes in the chorionic capillaries of 260 placentas examined in various ages of pregnancy, correlated with the weight in grams, length in centimeters, and the age in weeks.

## RESULTS

a. *Full-Term Infants (Weight Above 2,500 Gm.).*—Of the 260 placentas studied, 200 were in this group. The average weight of the infants was 3,377.6 Gm. and average length was 50.7 cm. Examination of the chorionic capillaries in the placentas of this group revealed absence of nucleated red cells in counting 1,000 erythrocytes in 166 placentas. In 33, one nucleated cell per 1,000 nonnucleated erythrocytes was found. Only in one case which was that of an asphyxia and in which the umbilical cord smear showed more nucleated red cells than are usually seen, we found 3 nucle-

ated cells in the chorionic capillaries per 1,000. The average count of nucleated red cells in the cord blood smears of these 200 infants was 7.3 per 100 leucocytes. This includes the five fatal cases with a much higher count of nucleated red cells in each (see Table III). In the majority of these cases the number of nucleated red cells ranged between zero and ten. Many of these were around 6; in 8 instances the count was above 10, varying between 12 and 24. Variations of weight and length of the infant had apparently no effect on this figure. In the microphotograph (Fig. 3, *A* and *C*), this very rare occurrence of nucleated red blood cells in the chorionic capillaries of a full-term placenta is shown.

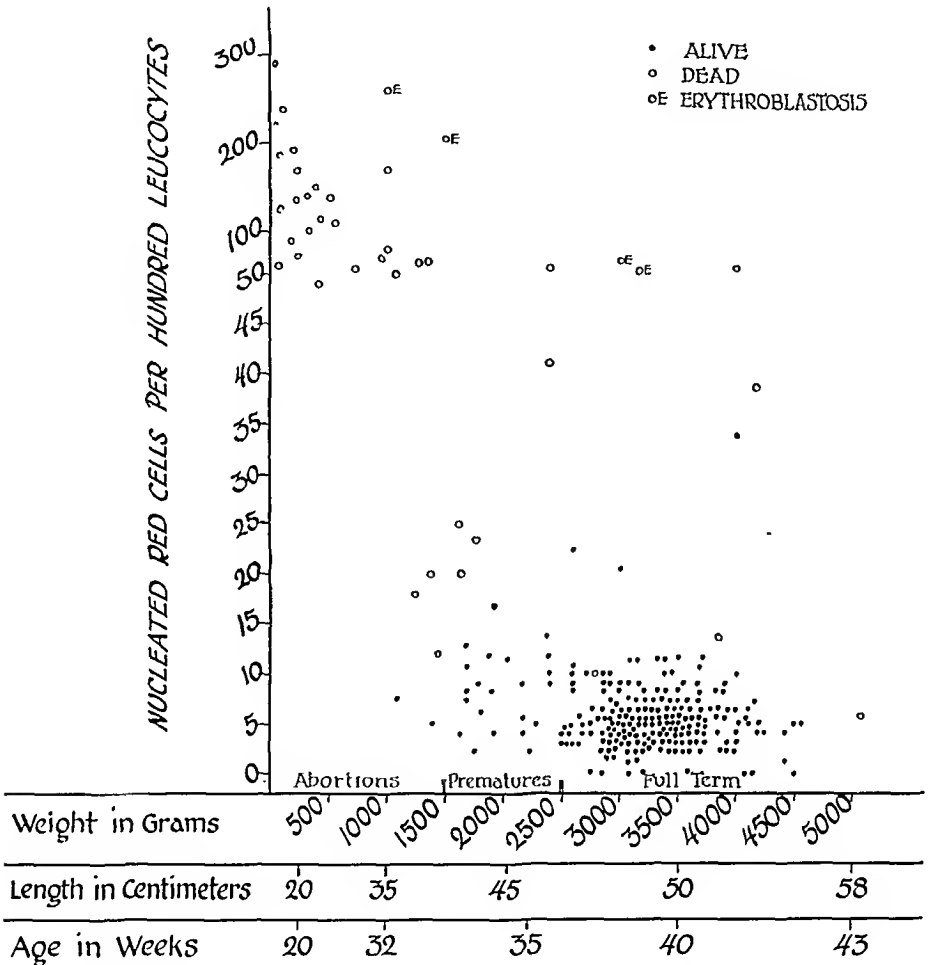


Fig. 2.—Scattergram, showing nucleated red cell counts per one hundred leucocytes in 260 cord blood smears of various ages of pregnancy, correlated with the weight in grams, length in centimeters, and the age in weeks.

b. *Prematures (From 1,500 to 2,500 Gm.).*—In this group, 30 cord smears and 11 placentas were studied. Twenty-five live infants had a nucleated red count of 11 per 100 leucocytes. The remaining 5, all of which died or were stillborn, had an average count of 57.3 per 100 leucocytes (Table III). This makes a total average of 21 nucleated red blood cells per 100 leucocytes. In 6 of the 30 placentas which were examined, the chorionic capillaries showed the presence of one nucleated red cell per 100 erythrocytes. In the other five, 2 per 1,000 erythrocytes were found.

c. *Abortions (under 1,500 Gm.).*—In this group, 49 placentas and 30 cord blood smears were examined. The results are recorded in Figs. 1 and 2. The average count for abortions is 101.7 nucleated red cells per 100 leucocytes. This figure, of

course, includes a wide variation in the age of pregnancy which was terminated by abortion and, as the accompanying graphs illustrate, counts as high as from 200 to 300 nucleated red blood cells per 100 leucocytes were found in the abortion of a twelve weeks' pregnancy. Correspondingly, we found values of 10 nucleated red blood cells per 1,000 erythrocytes in the chorionic capillaries in these cases in which the pregnancy was about three months of age. This value increased rapidly

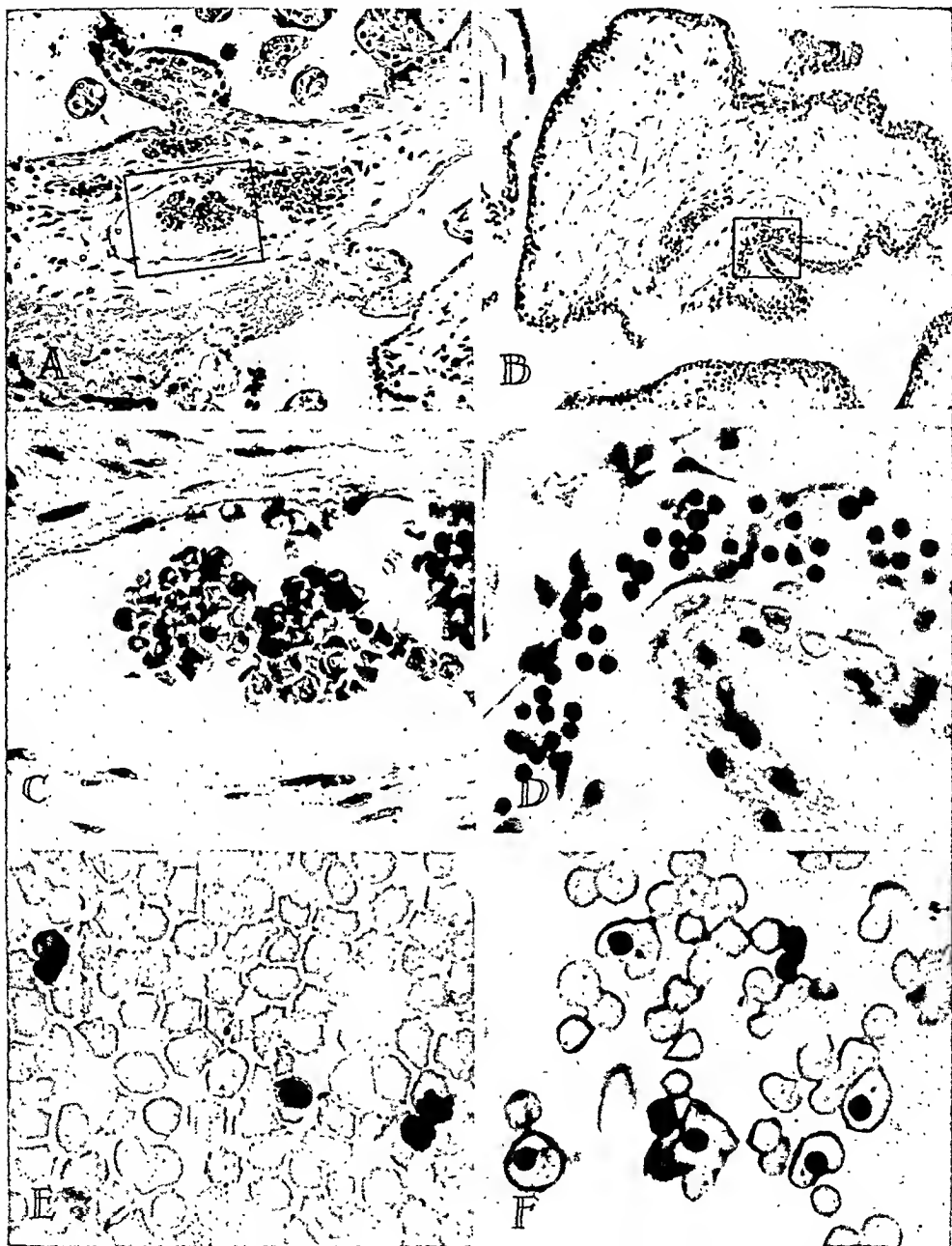


Fig. 3.—(A) Section through the placenta, illustrating the chorionic capillary of a full-term infant (low power). (B) Section through a chorionic villus of a six to eight weeks' pregnancy, illustrating the nucleated red blood cells in a capillary (low power). (C) The chorionic capillary of A, showing absence of nucleated red blood cells (oil immersion). (D) Chorionic capillary of the ink-marked area in B, showing numerous nucleated red blood cells. (E) Wright's stain preparation, showing nucleated red blood cells taken from a case of erythroblastosis. (F) Wright's stain preparation of nucleated red blood cells from a fetus of three months' gestation.



TABLE III. CAUSES OF DEATH AND NUCLEATED RED BLOOD CELLS PER 100 LEUCOCYTES AND 1,000 ERYTHROCYTES

CASE	NUC. R. B. C. CORD SMEAR	NUC. R. B. C. CHORIONIC CAP.	LENGTH (CM.)	WEIGHT (GM.)	AUTOPSY FINDINGS
<i>Full-Term Infants</i>					
M. K.	14/100	0/1000	52.0	3820	Intermeningeal and subdural hemorrhages. Tentorial tears. (Stillborn.)
D. S.	10/100	0/1000	55.0	2720	(Craniotomy.) Extensive maceration.
S. B.	38/100	0/1000	52.5	4210	Empyema (died on seventh day). Hemorrhages in kidney and scalp. Hemorrhagic pleuritis.
G. M.	6/100	0/1000	50.0	5280	Cephalematoma (stillborn). Atelectasis of both lungs. Autolytic fetus.
B. G.	54/100	0-1/1000	51.0	2530	Asphyxia (died 1 hour after birth). Diffuse hemorrhages in adrenals and both lateral ventricles.
	23.2/100	>1/1000	51.7	3712	Average
<i>Premature Infants</i>					
M. L.	72/100	2/1000	42.5	2450	Aspirated mucus in major bronchus. Subperiosteal hematoma and scalp hemorrhage. Atelectasis of both lungs. (Lived 7 hours.)
F. A.	68/100	3/1000	38.0	1620	Fetal atelectasis. (Stillborn.)
L. A.	74/100	2/1000	40.0	1560	Tentorial tears. Intermeningeal and pleural hemorrhages. Atelectasis (lived 2 days).
G. R.	41/100	1/1000	48.1	2480	Intratentorial and intermeningeal hemorrhages. Also hemorrhages in lungs.
A. G.	22/100	0/1000	37.0	1520	Acrania and anencephaly. Encephalocele.
	57.3/100	2/1000	41.2	1926	Average

in the abortions of younger age, until in those very early pregnancies from six to eight weeks' duration, practically all of the red blood cells in the chorionic capillaries were found nucleated (Fig. 3, *B* and *D*). A representative cord smear from a three months' fetus is illustrated in Fig. 3, *F*. However, in this same series of two infants, weighing 1,400 and 1,100 Gm., we found only 7 and 5 nucleated red cells per 100 leucocytes in the cord smear. These infants remained alive.

d. *Twin Infants*.—There were three sets of twins in this series. Their average weight was 2,665 Gm.; their average length 46 cm. Five nucleated red cells per 100 leucocytes were seen in the cord blood smear, and no nucleated red cells were found in the chorionic villi.

e. *Race*.—There are 17 negro infants in this series. Their average weight was 3,153.7 Gm., and their length 49.4 cm. The average nucleated red count per 100 leucocytes was 7. No nucleated red cells were found in the chorionic capillaries.

f. *Mortality*.—The mortality rate is 2.5 per cent for the 200 full-term infants. Post-mortem findings are tabulated in Table III. These findings are not complete, especially in the premature group. In some cases, it took many days until a post-mortem consent could be obtained. In these and in others, an extreme autolysis of

the tissues at the time of autopsy prevented a reliable morphologic analysis. This applies also to the umbilical cords, and cord blood studies could not be made in some of these cases. As seen in Table III, a distinctly increased number of nucleated red cells was found in the cord blood of the dead infants in each group.

*g. Maternal Statistics.*—The average age of the mothers in this series was 25.2 years. Eighty-three of these were primiparas, with an average age of 22.4 years. No variations in the nucleated red blood cell count were observed relative to parity or age of the mother. The average weight of the mothers at the time of delivery was 152.4 pounds; the average weight gained during pregnancy was 25.0 pounds. No difference was observed relative to the weights or the weight gained in infants born of these mothers. The average count of nucleated red cells was 7.1 per 100 leucocytes. In addition, this count was apparently not altered by such complications as mitral stenosis, pre-eclampsia, hypertension, and syphilis. The average erythrocyte count of the mother on the day of admission was 3,895,000 with a hemoglobin of 77.6 per cent. No correlation could be found between the red cell count and hemoglobin of the mother and the nucleated red cell count in the cord smears. Our series includes 4 patients with severe anemia and 1 patient with myelogenous leucemia, all of whom delivered normal babies without alteration of the nucleated red cell count in the cord smears or in the placentas. Stimulated by the studies of Büngeler and Schwartz,<sup>12</sup> we have tried to correlate our blood studies with the length of labor and the method of delivery. As previously noted, variations in the count of primiparas and multiparas, as a group, were negligible. Our findings are listed in Table IV.

TABLE IV. METHOD OF DELIVERY AND AVERAGE NUCLEATED RED COUNTS PER 100 LEUCOCYTES

LENGTH OF LABOR	CASES	SPONTANEOUS	CASES	LOW FORCEPS	CASES	BREECH
Under 10 hours	49	6.9/100	21	5.2/100 leucocytes	2	6/100
10-20 hours	43	6.8/100	25	6.6/100	1	10/100
20-30 hours	18	7.8/100	12	10.3/100	1	6/100
30-40 hours	4	6.0/100	6	9.6/100	0	----
40-50 hours	3	5.0/100	6	9.8/100	0	----
Over 50 hours	1	5.2/100	3	8.1/100	0	----
	118	6.3/100 Average	73	8.3/100 Average	4	7.3/100 Average

The 5 deaths are not included in this analysis. However, we did not feel, in analyzing each of these cases individually, that the increased count of nucleated red cells which was found in each one was conditioned by the type of delivery. Our Table IV shows that there is no marked variation of the nucleated red cell counts dependent upon length of labor or method of delivery.

The average weight of the placentas in the full-term infants was 641.07 Gm. Weight, insertion of cord, infarcts, and length of cord were noted, but no correlation could be established between these findings and the nucleated red blood cell count. The length of the cord played no part except in one case. In this it measured 115 cm. and was found coiled about the baby's neck. It was felt that this finding was the cause of death from severe asphyxia. The number of nucleated red cells in this case was 50 per 100 leucocytes, but only 2 to 3 nucleated red cells were seen among 1,000 erythrocytes in the chorionic capillaries of the placenta of this case.

*Erythroblastosis:* We have had four cases of erythroblastosis in our series. The cord blood smears gave the following counts of nucleated red cells per 100 leucocytes: 260, 210, 74, and 56. In only one case was it possible to examine the placenta. In this, 142 nucleated red cells could be counted per 1,000 erythrocytes within the chorionic capillaries. Fig. 3E shows the typical findings in one of these cases with universal edema. In this case, the stillborn infant was already considerably autolytic. An exact morphologic analysis of the blood smear was impossible, but the nucleated red cells within the capillaries of the placenta could be readily enumerated.

## DISCUSSION

The conclusions of Ryerson and Sanes<sup>15</sup> as to the number of nucleated red cells in the chorionic capillaries were based on the ratio between nucleated red cells and erythrocytes. They were of especial importance in determining the early phases of pregnancy from four to twelve weeks' duration, and comparing such figures to all those obtained from placental tissue in pregnancies older than twelve weeks. For this determination it was entirely sufficient to enumerate 100 erythrocytes. In amplifying their studies, we have demonstrated that in late abortions, but especially in the placentas of premature and mature pregnancies, it is necessary to count at least 1,000 erythrocytes in order to find one or, in a few cases, more nucleated red blood cells. Obviously, the cord smear gives us a more easily accessible means of determining the relative number of nucleated red cells. The erythroblast-leucocyte ratio might be found distinctly increased in premature infants in certain malformations and in all infants with very severe asphyxia, but this increase of nucleated red cells is not as striking in the ratio of erythroblasts to erythrocytes in a histologic analysis of the chorionic capillaries. This, as Ryerson and Sanes<sup>15</sup> already have pointed out, might be of considerable diagnostic value, especially in cases of erythroblastosis. In one of our cases of erythroblastosis, 142 nucleated red cells were numerated per 1,000 erythrocytes. On the other hand, in cases of asphyxia, this ratio never exceeded 2 to 3 per 1,000 erythrocytes.

It has been stated already by Büngeler and Schwartz<sup>12</sup> that the value of routine hematologic examination, including cord smears, at the time of delivery, and especially applied to premature babies, lies in prognosis. Javert believes that a low count of nucleated red cells in full-term infants is indicative of a more mature hemopoietic system. Conversely, premature infants, on the basis of weight and length, may have an immature hemopoietic system.

One-third of the premature cases in Group II in Javert's paper shows entirely normal counts. In addition, in 20 per cent of the mature Group I no nucleated red cells were seen at all. In 32 per cent of the same group, consisting of babies of normal or even excessive size, the blood smear gave the "premature" picture. In several cases of Group II in which a post-mortem examination was performed, distinct pathologic changes, especially subarachnoid hemorrhages, were found.

In our own very limited post-mortem series, in all full-term infants, severe hemorrhages, caput succedaneum or cephalematoma were found. In two instances with nucleated red cell counts of 6 and 10, respectively, death had occurred apparently previous to delivery. There were extensive maceration and considerable hemolytic fluid in the pleural cavities. Craniotomy had to be resorted to in one, while in the other, in spite of severe maceration, small suffusions were seen in the scalp. In our premature group, in all cases exceeding the weight of 1,000 Gm., distinct evidence of birth injury was present: suggillation in the scalp, subperiosteal hematoma, tentorial hemorrhages, multiple petechial hemor-

rhages in the serous membranes, hemorrhages in the lung parenchyma, and, in one case, very severe malformation with a huge encephalocele and extensive rachischisis.

From our series, as well as from the findings of Javert,<sup>13</sup> and especially from those of Büngeler and Schwartz,<sup>12</sup> it seems evident that nucleated red blood cells are frequently absent. This applies not only to mature infants but, within certain limits, also to prematures. What the actual or best controlled number of nucleated red cells in the large normal material from entirely normal deliveries really is, we hesitate to state with too rigid figures. In all probability, slight variations between zero and 5 to 10 will continue to be found, in line with the biologic differences of individuals and of such individually conditioned events as the birth of a child. We are inclined to agree with Büngeler and Schwartz<sup>12</sup> as to the ever ready responsive ability of the normal bone marrow to tissue damage, with or without asphyxia. Certainly asphyxia seems to play an important causative role in this entire complex, in many cases. What all these figures really reflect is the state of the bone marrow at the time of or immediately following delivery; but we do not know whether the state of the bone marrow preceding the time of delivery is also reflected by these figures. It might be in the normal fetus close to, if not identical with, the count in a normal infant. If the bone marrow does react in some instances with liberation of an abnormal number of embryonic forms of red and white cells into the circulating blood, then we might remember that this is the very nature of any normal bone marrow, not only at the time of birth but occasionally also in adult life in reaction to some severe injury as, for instance, extensive hemorrhagic infarctions or other inner hemorrhages. It is the very nature of the bone marrow that it is always in an embryonic state. Such reactions are in line with the experience of Büngeler and Schwartz<sup>12</sup> who found this sometimes more pronounced in the premature group and especially in infants below 40 cm. in length and 1,000 Gm. of weight. If within one to three days these reactive forms disappear completely, we could hardly consider this fleeting phenomenon an expression of a premature state of the bone marrow. In every other respect, however, our figures seem to confirm the findings of Javert,<sup>13</sup> especially in regard to the average count of nucleated red blood cells found in the smears from the umbilical cords.

Some of the differences in the numbers of nucleated red cells, as encountered in the literature, might be due to mere technical features. Büngeler and Schwartz<sup>12</sup> and Javert<sup>13</sup> have called attention to the higher count of nucleated red cells in the cord blood and the quick drop of nucleated forms in the smear taken from the blood of the newborn infant within the first twelve to twenty-four hours, leading to their complete elimination within a very few days.

Quite reluctantly, we have added our own results to this problem of number and significance of nucleated red blood cells in the newborn infant at the time of delivery. Our material is admittedly small. Small also is the number of post-mortem examinations which could be used for this study, but notwithstanding this deficiency, we feel these find-

ings should be reported, as their correlation to the hematologic findings from the cord blood appears of some value. We wish to urge more complete recording and reporting of normal or pathologic findings in the newborn infant, but more so in the stillborn, especially in such instances in which an abnormally high nucleated red blood cell count was seen in the cord smear and, reversely, also in those cases in which this count was not increased, as these might prove just as important. In addition, all such cases seem to be of great interest in which an unusually high number of nucleated red cells is encountered in the blood smear in an otherwise normally appearing infant. This blood smear might have a frank erythroblastosis-like appearance and still the anticipated change for the worse does not take place. Within a few days, the count returns to normal. We had such an experience recently.

A primipara was delivered of a full-term baby boy of 4,240 Gm. in weight and 53 cm. in length. The number of nucleated red cells on the day of delivery was 950 per 100 leucocytes, on the third day 104 per 100 leucocytes, and on the fifth day 55 per 100 leucocytes. The most interesting feature regarding this unusually high number of nucleated red cells is the fact that the labor had lasted for over seventy-four hours. But, as far as we know, the baby's subsequent development was normal.

Whether or not we should consider this recent experience of ours as exceptional, we believe as before in the great value of the cord blood smear in detecting cases of erythroblastosis.

Wintrobe and Schumaker<sup>18</sup> have compared the blood picture of patients with pernicious anemia during the response to liver therapy with the blood of the fetus. Liver extract has been used experimentally (Wintrobe<sup>19</sup> on this basis in rabbits), but it failed to bring about an increase in the blood values. Wigodsky and Ivy<sup>20</sup> working with rats, Bruner,<sup>21</sup> and Reimer,<sup>22</sup> who repeated these experiments with chick embryos, also failed in detecting any changes in the blood formation of the embryo. Recently Jones<sup>23</sup> has observed changes in the primitive blood formation of an eleven-day rat embryo, following parenteral administration of liver extract to the mother. He repeated these experiments with diets containing desiccated hog's stomach, and this also influenced embryonic erythropoiesis. Schlicke<sup>24</sup> fed pregnant albino rats with human gastric juice. This produced a significant increase in the number of nucleated erythrocytes, but it had no effect on the relative number of reticulated or nucleated red blood cells of the newborn.

We believe that the answer to these problems might have a direct bearing on a better understanding of several blood dyscrasias, not only of the newborn infant but of the adult as well. The experimental study of the nucleated red cell in embryonic life may prove a useful adjunct in the development of therapeutic agents in the future.

#### CONCLUSIONS

1. Systematic histologic study of the chorionic capillaries of placentas of various ages gave the following results as to the relative number of nucleated red cells:

- a. In early pregnancies (up to the sixth and seventh week), practically all of the red blood cells are nucleated.
- b. By the twelfth week, values of 10 or less nucleated red blood cells per 1,000 erythrocytes were counted.

c. In full-term pregnancies, one or two nucleated red blood cells per 1,000 erythrocytes were found in the chorionic capillaries of the placentas in 16.5 per cent of our series. In the remaining 83.5 per cent, no nucleated red cells were seen, counting 1,000 erythrocytes.

2. The results of our hematologic cord blood smears relative to the ratios of nucleated red blood cells to 100 white cells were as follows:

a. In early and late abortions, variations between 10 and 300 per 100 leucocytes, with an average of 101.7 nucleated red blood cells per 100 leucocytes, were found.

b. In premature infants, 21 nucleated red cells per 100 leucocytes were observed.

c. In full-term babies, 7.3 per 100 leucocytes were found.

3. Age, weight, weight gain, parity, blood pressure level, complications of pregnancy, including anemias, did not seem to affect this ratio.

4. Variations of weight and length of the fetus within the two groups of premature and mature babies did not influence the ratio.

5. In twins the average count was distinctly lowered.

6. In stillbirths and babies which died within the first ten days of life a higher nucleated red cell count was observed.

7. In babies with congenital abnormalities, and especially in severely dyspneic babies, higher nucleated red cell counts were found.

8. The nucleated red blood cell-leucocyte ratio was considerably altered in many babies in this series, but this was not so with the nucleated red blood cell-erythrocyte ratio in the same babies; however, in all cases of erythroblastosis, the marked increase of nucleated red blood cells was reflected in both ratios.

9. Cord blood smears and examination of chorionic capillaries are most useful in detecting cases of erythroblastosis.

10. A decided increase of nucleated red cells, in our opinion, points to pathologic states or events in the newborn infant, occurring during the course of delivery (the "birth crisis" of Büngeler and Schwartz<sup>12</sup>). This applies especially to asphyxia and its associated hemorrhages (birth injury in the broadest sense).

11. The cord blood smear is of decided prognostic value as to life, especially in the premature infant.

12. Nucleated red counts closely approaching or identical with that of the normal adult should be considered as the ideal physiologic blood count of the newborn infant. We feel that such a count is consistent with a normal, easy delivery, a normal state of the bone marrow in the premature as well as the full-term infants, with absence of any birth injury.

I am deeply indebted for the untiring effort and sincere interest of Drs. Kornel Terplan and F. C. Goldsborough, under whose direction this study was attempted. In addition, the splendid cooperation of Mrs. Alice Busch and Mr. Melford Diedrick in the preparation of data and photomicrographs, and the aid and suggestions of the many interns, nurses and students of the Department of Obstetrics of the Buffalo General Hospital, have been invaluable and sincerely appreciated.

#### REFERENCES

- (1) Neumann, E.: Arch. f. Heilk. 12: 187, 1871. (2) Lippman, H. S.: Am. J. Dis. Child. 27: 473, 1924. (3) Fischel, R.: Arch. f. Kinderh. 15: 470, 1890. (4) Loos, J.: Jahrb. f. Kinder. 29: 331, 1895. (5) Geissler and Japha, quoted

from Lippman: *Am. J. Dis. Child.* 27: 473, 1924. (6) *Heimann, F.*: *Ztschr. f. Geburtsh. u. Gynäk.* 69: 165, 1911. (7) *Karnitzki, A.*: *Arch. f. Kinderh.* 36: 42, 1904. (8) *Buchan, A. H., and Comrie, J. D.*: *J. Path. & Bact.* 13: 398, 1909. (9) *Rautmann, H.*: *Beit. path. Anat.* 54: 332, 1912. (10) *Schridde, H.*: *München. med. Wehnschr.* 57: 397, 1910. (11) *Kleinschmidt, H.*: *Klin. Wehnschr.* 9: 1951, 1930. (12) *Büngeler, W., and Schwartz, R.*: (a) *München. med. Wehnschr.* 74: 1822, 1927; (b) *Frankfurt. Ztschr. f. Path.* 35: 165, 1927. (13) *Javert, C. T.*: *Am. J. Obst. & Gynec.* 37: 184, 1939. (14) *Hellman, L. M., and Hertig, A. I.*: *Ibid.* 36: 137, 1938. (15) *Ryerson, C. S., and Sanes, S.*: *Arch. Path.* 17: 648, 1934. (16) *Ohringer, L.*: *Centralbl. f. allg. Path. u. path. Anat.* 63: 373, 1935. (17) *Halpert, B., and Stasney, J.*: *Arch. Path.* 26: 1045, 1938. (18) *Wintrobe, M. M., and Schumaker, H. B., Jr.*: *J. Clin. Investigation* 14: 837, 1935. (19) *Wintrobe, M. M.*: *A. J. M. Sc.* 193: 449, 1937. (20) *Wigodsky, H. S., and Ivy, A. C.*: *Proc. Soc. Exper. Biol. & Med.* 38: 787, 1938. (21) *Bruner, H. D.*: *Ibid.* 41: 260, 1939. (22) *Reimer, L.*: *Arch. f. exper. Path. u. Pharmakol.* 189: 656, 1938. (23) *Jones, O. P.*: *Arch. Int. Med.* In press. (24) *Schlicke, C. P.*: *Am. J. M. Sc.* 20: 155, 1940. (25) *Vierordt, K.*: *Gerhardt's Handbuch d. Kinderh.* 1: 53, 1877. (26) *Elder, G., and Hutchinson, R.*: *Edinburgh M. J.* 41: 105, 1895. (27) *Carstanjen, M.*: *Jahrb. of Kinderh.* 52: 215, 1900. (28) *Aiken, J.*: *J. Obst. & Gynaec., Brit. Emp.* 1: 414, 1902. (29) *Fehrsen, A. O.*: *J. Physiol.* 30: 332, 1903. (30) *Takasu, K.*: *Arch. f. Kinderh.* 39: 346, 1904. (31) *Grawitz, E.*: *Klin. Path. d. Blut., Leipsiz Thieme.* (32) *Biffi and Galli*: quoted from Lippman: *Am. J. Dis. Child.* 27: 473, 1924. (33) *König, H.*: *Folia Haematol.* 9: 278, 1910. (34) *Slawik, E.*: *Ztschr. f. Kinderh.* 25: 212, 1920. (35) *Lucas, W. P., Bradford, F. D., et al.*: *Am. J. Dis. Child.* 22: 525, 1921. (36) *Heath, E.*: *Bull. Buffalo Gen. Hosp.* 4: 42, 1926. (37) *Forkner, C. E.*: *Bull. Johns Hopkins Hosp.* 45: 75, 1929. (38) *Salomonsen, L.*: *Ztschr. f. Kinderh.* 51: 181, 1931. (39) *Cohen, P., and Shapiro, L. M.*: *M. Clin. of North America* 23: 581, 1939. (40) *Wolf, S., and Neigus, I.*: *Am. J. Obst. & Gynec.* 40: 31, 1940.

## INTRAUTERINE RESPIRATION IN RELATION TO DEVELOPMENT OF THE FETAL LUNG

WITH REPORT OF TWO UNUSUAL ANOMALIES OF THE RESPIRATORY SYSTEM  
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**A**NIMAL experiments carried on by several investigators during the past few years have shown beyond doubt that respiratory activity on the part of the fetus can occur in utero. One group believes that this activity is always present and that it plays an active part in the normal development of the pulmonary alveoli. Another group believes that respiratory activity is not physiologic and does not occur unless abnormal conditions exist.

This paper briefly reviews the work leading to these contradictory conclusions, presents a brief description of alveolar development and subsequent alveolar expansion, and reports two congenital anomalies which indicate that the inflow and outflow of amniotic fluid is not essential for normal alveolar development.

### SUMMARY OF LITERATURE

Snyder and Rosenfeld,<sup>1</sup> working with rabbits and other animals, and Barcroft and Barron,<sup>2</sup> using sheep, have definitely shown that, with the conditions under which they worked, movements of the chest wall similar to those normally asso-

ciated with respiration occur before birth. These movements are visible through the uterine wall but are better observed when the abdomen is opened in a saline solution at body temperature and the fetuses are delivered into the bath, the placental circulation being kept intact. If India ink is added to the water bath, the ink may be demonstrated in the alveoli of the fetuses that have exhibited respiratory movements,<sup>3</sup> definitely indicating that the rhythmic respiratory movements can result in an exchange of amniotic fluid between the alveoli of the unborn animal and the amniotic cavity.

These respiratory movements commence early in pregnancy, and Snyder and Rosenfeld<sup>4</sup> believe that in addition to being a normal function of the fetus they play a major role in the development of the lungs. The statement is made that any impediment to the inflow of amniotic fluid will affect the development of the alveoli, resulting in atelectasis. According to the authors, "Fetal respiration aids in the structural differentiation of the normal lung. The normal development of the alveoli may be complicated by the presence of amniotic fluid containing debris of excessive amount or abnormal type. A mechanical obstruction of bronchioles brought about during embryonic life may interfere with the normal flow into the lung of amniotic fluid and result in incomplete dilatation of alveoli; i.e., atelectasis."<sup>4</sup> Also, "There is evidence that intrauterine respiration is of functional significance in the development of a normal lung, aiding in dilatation in alveoli and elastic walls of the future air passages."<sup>3</sup>

Windle and his co-workers,<sup>5, 6</sup> on the other hand, insist that any operative procedure involving the uterine wall immediately initiates abnormal changes in the fetal environment and that these changes interfere with the normal maternal-fetal oxygen exchange, so that the action of the fetus under such circumstances cannot be considered normal. He believes that although respiratory movements of the chest can occur, they are not found under normal conditions and do not always result in aspiration of amniotic fluid into the alveoli. His conclusions are based on experiments in which he injected thorotrast into the amniotic cavity of unanesthetized, unoperated guinea pigs and then observed them with periodic x-rays. The thorotrast could be demonstrated in the fetal lungs only when abnormal conditions such as anoxemia or dystocia existed.

The fact that the fetuses observed by Snyder and Rosenfeld breathed normally and survived after they were removed from the water bath and the cord severed, and that various animals exhibited a uniform response while in the bath to changes in oxygen, carbon dioxide or drug content of the maternal blood, indicate that these authors must be fairly correct in their assumption that the environment of the animals is not greatly altered by the operative procedures.

To what extent these animal experiments may be considered indicative of similar activity on the part of the human fetal lung has not yet been proved. By carefully observing the abdomen of a pregnant woman, rhythmic movements can occasionally be seen,<sup>7, 8</sup> which are independent of maternal movements and are believed due to fetal breathing. A few attempts have been made to identify radio-opaque material in the human fetal lung following its introduction into the amniotic fluid of pregnant women. Reifferscheid and Schmeimann<sup>9</sup> injected ambrothor into the amniotic fluid of women whose pregnancies were about to be interrupted. By fluoroscopy before operation and by microscopic examination after death, they demonstrated the substance in the fetal lungs. They described it as moving rhythmically back and forth in the bronchial tree and stated that they could demonstrate it as early as the fourth or fifth month of pregnancy.

Windle,<sup>5</sup> however, mentions 6 cases studied in a similar manner by Dr. Cornell in which diotrast, injected into the amniotic cavity, could not be demonstrated in the fetal lungs. Bufe<sup>11</sup> delivered one of a pair of human twins at six months' gestation into a water bath at cesarean section and was unable to elicit respiratory movements until the oxygen content of the fetal blood was diminished. He states that by taking roentgenograms of other fetuses in utero at few second intervals over periods of several hours he was able to convince himself that movements of the thoracic cage did not occur.

It should be noted that the technical difficulties involved in studying the human fetus are great, and one must be very cautious in drawing definite conclusions relative to the respiratory activity of the human fetus at the present time.



Microscopic examination of the lungs of stillborn fetuses and infants dying a few hours or days after birth frequently reveals the presence of squamous epithelial cells desquamated from the fetal skin, vernix caseosa and material from the fetal intestinal tract in the alveoli. These substances cannot be demonstrated in all cases and this fact has led to the belief that their presence is abnormal. They have most generally been considered a result of stimulation of the respiratory center by decreased oxygenation of the blood while the fetus was still in utero, and have been considered a sufficient basis for the diagnosis of intrauterine asphyxia.<sup>11, 12</sup> Those who believe this material is constantly present in the alveoli explain its apparent absence as being due to marked dilution which may result from an increase of amniotic fluid, from decreased amounts of solid particles in the fluid, or from both. They also believe that its distribution in the lungs may be patchy and that if a sufficient number of sections are examined the amniotic elements almost invariably can be seen. If this conception is true, the old idea that amniotic fluid in the lung is an indication of asphyxia must be abandoned, and the fluid must be considered a normal physiologic constituent. In any event, the presence of amniotic elements is definite evidence that amniotic fluid can enter the human fetal lung and that it probably does so as a result of active inspiratory movements.

#### LUNG DEVELOPMENT

The alveoli in the fetal lungs develop as solid masses of cells which grow, become canalized, and subsequently resemble small hollow balls lined by large cuboidal cells. Increase in alveolar caliber is due, in early fetal development, to multiplication of these cuboidal cells, but later it is brought about largely by the invasion of capillaries derived from the underlying blood vessels into this originally continuous lining.<sup>12</sup> The capillaries force their way inward between the cells, so that at term the alveolar lining is composed of naked capillaries with the original cuboidal cells persisting only in the small spaces between them. The alveolar walls are thus greatly increased in surface area and are given a uniformly irregular appearance somewhat similar to that of partially crumpled paper sacks (see Fig. 4).

With the expansion which follows initiation of respiration after birth, the slack is gradually taken up, the alveolar walls become much less irregular in pattern, and the alveolar volume is greatly increased. The change from an unexpanded to an expanded state is a gradual process that requires several days for completion.

The lung which has never contained air is generally described as being atelectatic, but when used in this connection, the term is misleading. It is usually used to indicate collapse of alveoli with obliteration of all lumina, and in this sense is not true of the fetal lung. The alveoli become larger and modified in shape with progressive intrauterine development, but the walls are never collapsed and after the first few months a lumen is normally present in each alveolus. Since a lumen is present, something must fill the space; it cannot be air and it must, therefore, be fluid. Two sources are possible: aspiration of the media in which the fetus is immersed or transudation of body fluid through the alveolar walls. As mentioned previously, Snyder and Rosenfeld believe it is the former and that it is necessary for normal development. Evidence derived from a study of the malformations to be described shows that it can be the latter and that normal lung development may occur without the inflow of amniotic fluid.

## DISCUSSION

A well-known pathologic state exists in the hypoplasia of lung tissue which is associated with failure in development of the diaphragm and herniation of the abdominal viscera into the thoracic cavity. Both lungs are almost always smaller than normal but the greatest reduction in size occurs in the one on the same side as the diaphragmatic defect. The histologic structure of these lungs is most interesting. Instead of exhibiting alveoli histologically normal for the period of gestation at which the fetus is delivered, the lungs manifest a state of immaturity comparable to that found in a more immature fetus whose lungs normally would be of such size and weight. The small size is not due to collapse of alveoli; instead, cuboidal epithelial cells form a proportionately greater part of the alveolar walls and capillary ingrowth has been arrested so that alveolar development is incomplete. The degree of hypoplasia exhibited histologically is comparable to the degree of immaturity visible grossly.

Lungs even more hypoplastic may be found occasionally in association with massive pleural effusions. In one case, a fetus 45 cm. in length recently observed at the Chicago Lying-in Hospital, the combined weight of the lungs was 3.6 Gm. (average for a fetus of this size is 44.2 Gm.). We have seen several other cases with similar but somewhat less marked hypoplasia from the same cause. In all of these cases the pleural effusion must have developed in the first few months of fetal life in order to have arrested lung development at such an early stage. The histologic immaturity of these lungs, as well as that associated with diaphragmatic hernias, is approximately equivalent to that found in lungs of equivalent size in normally developed premature fetuses.

The immaturity of the lungs associated with diaphragmatic defects or pleural effusion might be due to a direct inhibition of growth caused by lack of space for development, or it might be secondary to a lack of space for the inflow and outflow of amniotic fluid. This question cannot be answered from these cases.

We have recently observed two different anomalies which add materially to our knowledge. The first was observed on our own service and the second was very kindly sent to us by Dr. Aaron Gunther who performed the autopsy.

In the first of these (Fig. 1), a mass of lung tissue was found in the left pleural cavity which had no connection with the trachea and into which, therefore, amniotic fluid could not enter. It was present in an infant with an associated left-sided diaphragmatic hernia, and the three divisions of lung tissue (right, left, and accessory lungs) showed an extremely interesting histologic pattern which is described in the autopsy protocol at the end of the paper. The unconnected mass of lung tissue (Fig. 2) and the right lung are composed of alveoli similar to the expected appearance in an infant at term, while those in the left lung are modified by the existence of the diaphragmatic hernia. Why the accessory lung should not have been more greatly compressed and more inhibited in its development is difficult to understand. It may possibly have been protected from direct compression by its location in a pocket

behind the heart. At any rate, although it was entirely impossible for amniotic fluid to have entered the alveoli, the alveolar spaces were large and the walls normally developed.

In the second infant (Fig. 3) tracheal obstruction resulted from a malformation of the cricoid cartilage. The obstruction was complete except for a minute canal approximately 1 mm. in circumference located behind the cartilaginous mass which produced the occlusion. It formed the only connection between the larynx above and the trachea below. The lungs were large, well developed and entirely normal histologically (Fig. 4). Although there was a connection between the larynx and the trachea it was by a canal so small that its identity could be definitely established only with the aid of a dissecting microscope. One cannot deny the possibility that amniotic fluid in the pharynx might have leaked into the trachea and thence into the lungs, but it is inconceivable that such a minute opening would permit an inflow and outflow of amniotic fluid at a rate comparable to that at which intrauterine respiration is believed to take place. No debris which might have been derived from amniotic fluid was present in the alveoli of any of the sections studied.

Thus, in these two cases, normal alveolar development occurred despite the fact that in the first instance the alveoli had no connection whatever with the amniotic cavity and that in the second case there was a definite and marked impediment to the inflow and outflow of fluid which was of sufficient degree probably to prevent entirely the entrance of fluid into the lung.

#### CASE REPORTS

CASE 1.—(FA-39-246.) A white male infant, weighing 3,380 Gm., was delivered naturally. It gasped several times but respiration could not be established and the heart ceased beating within a few minutes.

At autopsy the external appearance of the body was entirely normal. Inspection of the abdominal cavity revealed a defect in the left posterolateral portion of the diaphragm through which was herniated the left lobe of the liver, the spleen, and the greater part of the small intestine and colon. Inspection of the thoracic cavity showed the heart and mediastinal structures displaced to the right. The left lobe of the liver occupied a position immediately to the left of the heart, and lateral to this were the small intestine and colon. The spleen was posterior and lateral. The heart had undergone normal rotation but was displaced to the right. Upon removing the abdominal organs from the thoracic cavity, a mass resembling lung tissue (Fig. 1) was found anterior to the thoracic vertebrae and posterior to the heart in the space ordinarily occupied by the posterior mediastinum. The mass was covered with pleura and, except for blood vessels connecting it with the aorta and inferior vena cava, was free in the pleural cavity. It was in no way connected with a bronchus and received its blood supply directly from the thoracic aorta.

The histologic appearance of the right lung was approximately normal for an infant at term. The alveoli were lined by normal capillaries with a few intervening cuboidal cells. A few peripheral alveoli were expanded by air, but in the rest of the lung the alveoli were of the normal intrauterine caliber or were slightly compressed. Bronchi and alveoli were present in normal proportions.

The left lung was grossly and histologically hypoplastic. The appearance was similar to lung tissue from a very premature fetus, and alveolar development was very incomplete. In many areas the alveoli were small, were lined by a continuous layer of cuboidal epithelium or were present as solid masses not yet canalized. The major blood vessels, bronchi, and areas of cartilage were relatively increased in amount due to the incomplete elaboration of alveoli.

The mass of accessory lung tissue was very similar to normal non-aerated lung (Fig. 2). It was divided into lobules by loose connective tissue and contained normal appearing blood vessels, bronchi, and cartilage. The septa were slightly wider than usual due to a slight increase in connective tissue, but the caliber



Fig. 1.—Case 1. The tongue and trachea were removed intact. The cartilage (A) completely occluded the trachea, and in the specimen has been split through the center. The larynx and trachea ended in round pouchlike structures, the cut surfaces of which are visible above and below the cartilage. The minute canal connecting the trachea and larynx is visible at (B).

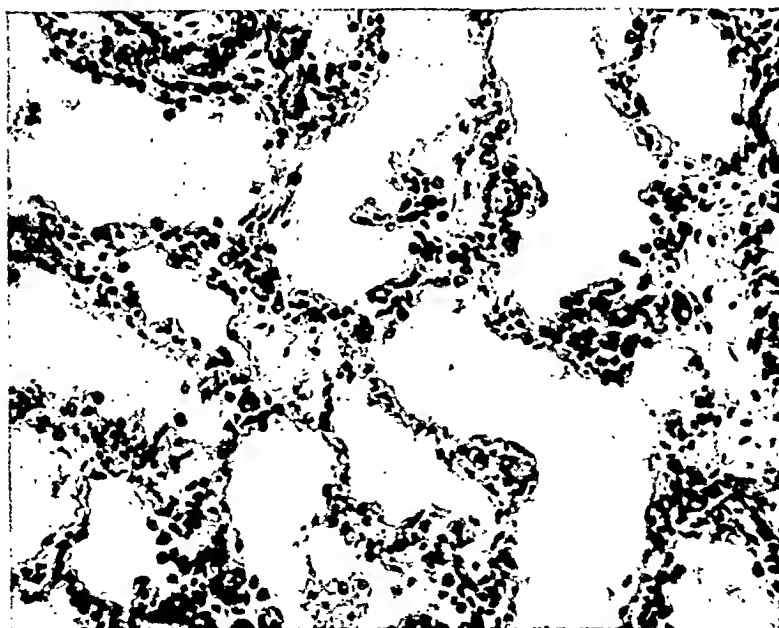


Fig. 2.—Histologic appearance of lungs from Case 1. The alveoli are normally developed. ( $\times 265$ .)

and shape of the alveoli were similar to normal lung. The lining of the alveoli consisted of capillaries with moderately numerous intervening cuboidal cells.

A number of cases of accessory lung can be found in the foreign literature, but few have been reported in the journals written in English. For further information the reader should see the papers of Guy and Rand,<sup>13</sup> Bert and Fischer,<sup>14</sup> and the general discussion of the subject in Abt's *Pediatrics*.<sup>15</sup>

CASE 2.—(FA-38-830.) A white male infant, weighing 2,630 Gm., was delivered naturally. He did not breathe and several unsuccessful attempts were made to pass a tracheal catheter. The heart ceased beating after twenty minutes.

At autopsy the external surface of the body and abdominal cavity were entirely normal. The pleural cavities, lungs, and mediastinum also appeared normal. The lungs, trachea, and tongue were removed as a single specimen, and on opening the trachea, a complete cartilaginous obstruction (Fig. 3) was found immediately below the larynx. This resulted from the imperfect formation of the cricoid cartilage which was present as a solid disc almost completely occluding the lumen of the trachea. It was not until the specimen was investigated under a dissecting microscope that a small canal approximately 1 mm. in



Fig. 3.—Case 2. The viscera have been removed from the thoracic cavity; the mediastinum has been drawn to the right and the accessory lung (A) has been taken out of the pocket (C) behind the mediastinum in which it was originally found. The blood vessel connecting the accessory lung with the aorta (D) is visible. The hypoplastic left lung is also present (B).

circumference and lined with mucosa was found posteriorly in the midline. This canal connected the two parts of the trachea and formed the only communication between the lungs and the amniotic cavity. The posterior plate of the cricoid cartilage was represented by a slight thickening of the posterior edge of the disc. The thyroid cartilage and vocal cords were both normal and the trachea below the obstruction was normal, except for a moderate decrease in the cartilage present in the tracheal rings. The lungs on cut section appeared uniform in character and fluid could be expressed from their substance.

Histologically, the lungs appeared entirely normal (Fig. 4), for an infant at term who had never inspired air. The alveoli were lined by capillaries and by irregularly distributed cuboidal cells identical with the normal pattern. The alveolar lumina were normal in size and shape. They contained a moderate

amount of precipitated protein material, indicating that fluid (probably a transudate) had been contained within them, but no vernix caseosa, desquamated epithelial cells or other debris from the amniotic fluid were present.

A study of the embryology of the larynx and trachea<sup>16, 17</sup> shows how this anomaly probably occurred. The laryngotracheal groove first appears in the 2.5 mm. embryo and runs lengthwise in the floor of the gut caudal to the pharyngeal pouches. This groove or ridge separates from the esophagus and becomes the larynx, trachea, and lungs. During the seventh week, the larynx is T-shaped and for a time ends blindly because of fusions of the laryngeal epithelium. This fusion varies in extent and may be complete or incomplete. Occasionally there is a fine canal that remains patent along the posterior wall of the larynx. In fetuses of ten weeks all union has disappeared. Rarely this occlusion persists and is seen at birth as a membrane or web fastened to the anterior and lateral walls and partially occluding the lumen. Our case represents a still more rare condition, in that the stenosis was cartilaginous and practically complete. The canal mentioned above also persisted.

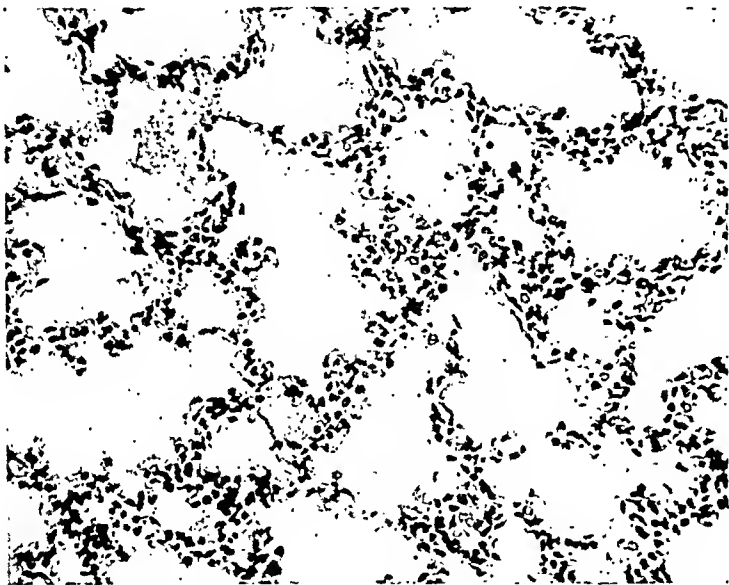


Fig. 4.—Histologic appearance of the lungs from Case 2. The alveoli are normally developed. (X265.)

Stenoses similar to the one reported here are rarely discovered, probably not so much because they do not occur as because they are incompatible with life and are not diagnosed. The incomplete stenoses are more common and usually permit adequate breathing. Many reports can be found in the literature<sup>18-20</sup> which discuss the etiology, diagnosis and treatment of the incomplete type.

#### CONCLUSIONS

1. A tidal flow of amniotic fluid in and out of the lungs is not necessary for normal alveolar development.
2. Hypoplasia of the lungs is probably caused by direct pressure on the lung parenchyma, the arrest of development being dependent on the degree of pressure suffered and the stage of development at which it is first applied.
3. There is sufficient evidence to permit the following statements:
  - a. Intrauterine respiratory movements occur in laboratory animals.
  - b. These respiratory movements can result in aspiration of the fluid in which the animal is immersed.

- c. Intrauterine respiratory movements occur in the human fetus.
- d. These respiratory movements can result in aspiration of the fluid in which the human fetus is immersed.

4. The evidence presented in the literature suggests, but does not prove, that intrauterine respiratory movements are a normal physiologic process.

The authors are greatly indebted to Dr. Aaron Gunther for the specimen of trachea and lungs which he removed at autopsy in Case 2.

#### REFERENCES

- (1) *Snyder, F. F., and Rosenfeld, M.*: Am. J. Physiol. 119: 153, 1937. (2) *Barcroft, J., and Barron, D. H.*: J. Physiol. 88: 56, 1936. (3) *Snyder, F. F., and Rosenfeld, M.*: Proc. Soc. Exper. Bio. & Med. 36: 45, 1937. (4) *Idem*: J. A. M. A. 108: 1946, 1937. (5) *Windle, W. F., Becker, R. F., Barth, E. E., and Schulz, M. R.*: Surg., Gynec. & Obst. 69: 705, 1939. (6) *Steele, A. G., and Windle, W. F.*: J. Physiol. 94: 531, 1939. (7) *Ahlfeld, F.*: Monatschr. f. Geburtsh. u. Gynäk. 21: 143, 1905. (8) *Reifferscheid, K.*: Arch. f. d. ges. Physiol. 140: 1, 1911. (9) *Reifferscheid, W., and Schmiemann, R.*: Ber. d. phys.-med. Gesellsch. z. Wuerzburg. 62: 202, 1939. (Reviewed Surg., Gynec. & Obst. Internal abstr. 71: 278, 1940.) (10) *Farber, S., and Sweet, L. K.*: Am. J. Dis. Child. 42: 1372, 1931. (11) *Bufe, W.*: Ztschr. f. Geburtsh. u. Gynäk. 113: 265, 1936. (12) *Potter, E. L., and Adair, F. L.*: Fetal and Neonatal Death, Chicago, 1940, The University of Chicago Press, p. 38. (13) *Guy, C. C., and Rand, G. L.*: Illinois M. J. 62: 61, 1932. (14) *Bert, P., and Fischer, B.*: Frankfurt. Ztschr. f. Path. 6: 27, 1911. (15) *Abt, Isaac A.*: Editor. Pediatrics, Philadelphia, 1924, W. B. Saunders Company 4: p. 27. (16) *Arey, L. B.*: Developmental Anatomy, Philadelphia, 1938, W. B. Saunders Company, pp. 210-211. (17) *Keibel, F., and Mall, F. P.*: Manual of Human Embryology, Philadelphia, 1912, J. B. Lippincott Company, 11: pp. 476-482. (18) *Wilkinson, R. W.*: J. A. M. A. 102: 1756, 1934. (19) *Clerf, L. H.*: Ann. Otol., Rhin. & Laryng. 40: 770, 1931. (20) *Tucker, G.*: J. A. M. A. 99: 1899, 1932.

### SUPRAVAGINAL AND TOTAL HYSTERECTOMY\*

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THE question so often mooted as to whether supravaginal or total hysterectomy should be routinely performed cannot be answered simply. In evaluating statistical studies, the characteristics of the staff and the geographical differences in the patient population must be considered. What raises the morbidity and mortality is the extent of the disease for which the operation is performed, if other things are equal. It is the unanimous answer of those men who have served in both Northern and Southern Clinics that the latter with their large colored and rural population produce by far the "grander" fibroids and the more "magnificent" inflammatory disease. Prolapse is also almost never seen among colored patients. The operation of supravaginal hysterectomy is often reserved for the patients that present the most difficult surgical problems. By keeping these points in view, it may be possible to arrive at a conclusion unbiased by the "totalists"

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erying carcinoma of the cervical stump or by the "subtotalists" erying high operative mortality and morbidity.

The present study represents an attempt to arrive at a conclusion for this particular medical community. Because of the predominantly colored population, and because they have been accused of being responsible for high mortality rates, the statistics have been analyzed for each race. All available records of those receiving either operation and all deaths from the opening of Duke Hospital in July, 1930, to July, 1940, have been included in the study. Seven hundred and ninety-four

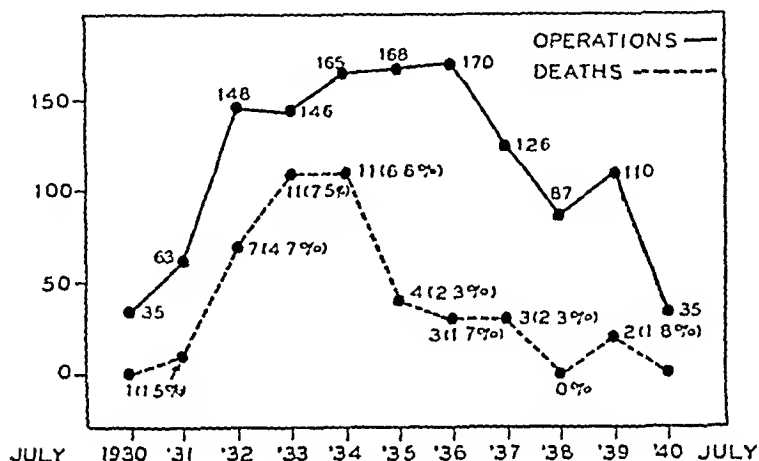


Fig. 1.

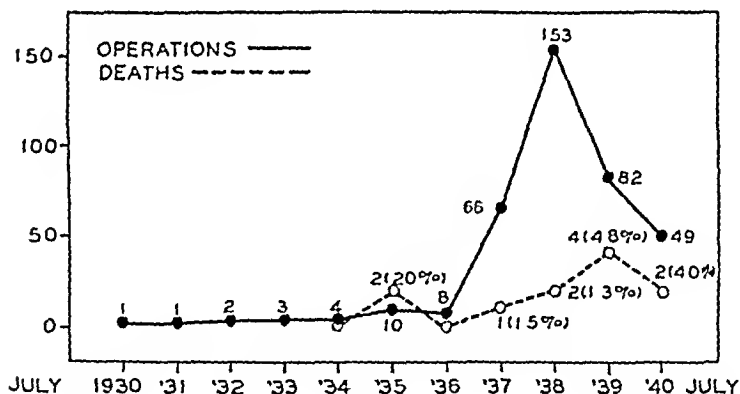


Fig. 2.

supravaginal hysterectomies and 148 total were performed on colored patients and 449 supravaginal and 225 total on white patients. Three hundred and eighty, or 21 per cent, of all operations were performed by the visiting staff and 344, or 90 per cent, of these by four men. The rest were operated upon by the house staff. This represents a total of 1,243 supravaginal hysterectomies, and 373 total hysterectomies. Prior to 1937 total hysterectomy was rarely performed for any indication other than carcinoma of the fundus. Following the trend of the times, after 1936, total hysterectomy has become almost a routine procedure on the



white patients. Largely for historical interest Figs. 1 and 2 were prepared, giving the number of patients who received operation and the mortality.

The gross mortality for supravaginal hysterectomy for the ten-year period was 3.4 per cent, for white patients 3.5 and for colored 3.3 per cent. The poor white patient with anemia, pellagra, and hypertension is no better operative risk than the anemic, obese colored patient, with

TABLE I. SUPRAVAGINAL HYSTERECTOMIES

PATHOLOGY	WHITE	COLORED	TOTAL	WHITE DEATHS	COLORED DEATHS	TOTAL DEATHS
Myoma	121	275	396	4	7	11
Myoma and infection	43	286	329	2	11	13
Infection	79	117	196	2	3	5
Normal tissue	22	16	38			
Flowing	16	10	26	1	1	2
Prolapse	46	1	47			
Previous operation	23	10	33	3		3
Hyperplasia	11	1	12			
Endometrial polyps	11	6	17			
Adenomyosis	12	6	18	1		1
Endometriosis	3	5	8			
Adenocarcinoma	3		3			
Proliferative cysts	16	12	28			
Dermoids	2	10	12			
Fibroma of ovary	4	4	8			
Therapeutic terminations	9	7	16	1	1	2
Porro sections	5	9	14	1	2	3
Tubal pregnancies	7	11	18			
Others	16	8	24	1	1	2
Totals	449	794	1,243	16	26	42

TABLE II. SUPRAVAGINAL HYSTERECTOMY FOR INDICATIONS OTHER THAN THOSE TABULATED

## White:

1. Follicle cyst with hemorrhage
2. Retention cysts
3. Retention cysts
4. Adenocarcinoma of the ovary
5. Imperforate anus and congenital rectovaginal fistula
6. Double uterus
7. Blastomycosis of tube
8. Question of brucella infection in pelvis
9. Hydatidiform mole
10. Rhabdomyoma of uterus
11. Granulosa cell tumor of ovary
12. Granulosa cell tumor of ovary
13. Sarcoma arising from myoma
14. Chorioepithelioma of the tube
15. Broad ligament cysts
16. Broad ligament cysts

## Colored:

1. Postoperative cervicovesicovaginal fistula
2. Tuberculosis of endometrium and myometrium
3. Adenocarcinoma and sarcoma of the uterus
4. Postoperative menstrual fistula
5. Cyst of the uterus
6. Cyst of the uterus
7. Teratoma of the ovary
8. Parovarian cysts and torsion

extensive pelvic inflammation. The gross mortality for total hysterectomy was 2.9 per cent, 2.2 per cent for white, and 4.4 per cent for colored patients. The difference will probably be explained because of the difference in vaginal flora of the two races.<sup>1</sup>

As in most larger clinics an attempt was made to perform the hysterectomies on patients who really needed them. Sixty-four per cent of the patients of each series received hysterectomy for myoma, myoma and infection, and infection. Tables I to IV give the pathologic bases for the procedures.

TABLE III. TOTAL HYSTERECTOMY

PATHOLOGY	WHITE	COLORED	TOTAL	WHITE	COLORED	TOTAL
				DEATHS	DEATHS	DEATHS
Myoma	54	35	89	1	1	2
Myoma infection	17	58	75		2	2
Infection	33	23	56		2	2
Normal tissue	2		2			
Flowing	10	1	11	2		2
Prolapse	31	1	32	1		1
Previous operation	8		8			
Hyperplasia	7		7			
Endometrial polyp	2	2	4			
Adenomyosis	6	4	10			
Endometriosis	2		2			
Adenocarcinoma	16	4	20	1		1
Proliferative cysts	10		10			
Dermoid	1	5	6			
Therapeutic terminations	10	7	17			
Tubal pregnancies	5	1	6			
Other	9	4	13		1	1
Carcinoma of cervix	2	3	5			
Totals	225	148	373	5	6	11

TABLE IV. TOTAL HYSTERECTOMY FOR CAUSES OTHER THAN THOSE TABULATED

## White:

1. Metaplasia of the cervix
2. Previous pyometra
3. Carcinoma of the ovary
4. Fibrosarcoma of the ovary
5. Teratoma of the ovary
6. Congenital stenosis of the vagina
7. Congenital stenosis of the vagina
8. Bicornuate uterus
9. Double vagina, one stenotic, and double cervix

## Colored:

1. Ruptured uterus
2. Ruptured uterus
3. Chorioepithelioma
4. Granulosa cell tumor of ovary

Those patients on whom the pathologist sent back the report of "normal" represent the class that received operation for such things as epilepsy occurring with the menses, severe dysmenorrhea in elderly spinsters, etc. A number of patients had a hysterectomy for flowing of considerable severity, uncontrollable by conservative means. The endometrium showed an entirely normal pattern and in some cases

was atrophic. Abdominal hysterectomy of either sort was used with diminishing frequency for prolapse. With such excellent operations as the Manchester and vaginal hysterectomy, the old formidable, time-consuming double procedure has become less frequently necessary.

There is another class of patients that deserves special mention, those that had been victims of piecemeal surgical procedures on pelvic organs. One patient had had six previous abdominal operations, apparently for retroversion and retention cysts. These patients have multiple pelvic complaints, and when the tissue removed by hysterectomy is reported, it is normal. More harm has been done by the performance of suspensions and meddlesome operations on infected patients than can ever be explained away in another generation. A suspension is never indicated and the "all-or-none" law should be followed in operating on inflammatory conditions if conservative management fails. Unfortunately piecemeal surgery is not performed in large clinics with critical house staffs, open staff meetings, and qualified visiting men. An institution of the United States Navy might be advantageously adopted by the medical profession and everybody in a manipulative branch of medicine be subjected to the scrutiny of a "fitness report." In the medical profession it should consist of a list of the operations performed with the report of a scrupulous pathologist on the tissue removed. This would soon stop the morning routine prevalent in so many institutions of operating on the "chronic cervicitis, chronic appendicitis, and retroversion" syndrome. The other classifications require no explanation. The three supravaginal hysterectomies for adenocarcinoma of the fundus were done because of technical difficulties in removing the cervix.

There were relatively few operations performed for proliferative cysts. Dupertuis, and Zollinger<sup>2</sup> in their survey of 1,000 hysterectomies done on a general surgical service, reported 632 supravaginal and total hysterectomies for myomas and 243 for cysts. In the present series the number of operations performed for retention cysts, corpora lutea, etc., is rather small.

The treatment of the adnexa during the past decade varied bewilderingly according to the operator. Usually the ovaries were not conserved in patients with infection. One operator made it routine to remove the adnexa completely with every hysterectomy. The others left one or both ovaries usually. Two of the retained ovaries required subsequent removal and one patient died following the procedure. The appendix was removed routinely from all patients in whom the blood loss had not been great nor the operation too long. Two of those that retained their appendix required subsequent operation for acute appendicitis four years later. Plastic procedures on the vagina were carried out rarely with any except the patients operated upon for prolapse. Drainage was rather frequently employed in this clinic, and about 18 per cent of those having supravaginal hysterectomy had abdominal drainage. About 22 per cent of those receiving total hysterectomy had vaginal drainage. If the drains were primarily hemostatic, to control

the bleeding or oozing from frayed peritoneal surfaces they were removed in forty-eight hours; if for frank sepsis, they were removed after seven days.

The anesthesia used is given in Table V.

TABLE V. ANESTHESIA

	GAS-OXYGEN- ETHER	ETHER	NOVOCaine SPINAL	NOVOCaine AND INHALATION	PONTOCaine SPINAL	PONTOCaine AND INHALATION	CYCLOPROPANE
Supravaginal	807	153	132	60	76	8	9
Avertin with inhalation 4, local 1, vinethene and ether 1							
Total	150	47	2		131	14	28
				Epidural 1			

Novocaine spinal anesthesia was uniformly rather unsatisfactory both because of disconcerting fluctuations in blood pressure and because of the shortness of duration. Forty-four per cent of the patients receiving novocaine spinal anesthesia required supplementary inhalation anesthesia. The latter part of 1937 Dr. E. R. Rucker, an assistant resident, introduced the use of pontocaine and glucose spinal anesthesia as described by Sise<sup>3</sup> of the Lahey Clinic. This anesthesia has proved very satisfactory for either total or supravaginal hysterectomy. There are very few unpleasant vascular sequelae and the duration is usually ample. Only 10 per cent of the pontocaine spinal anesthetics required any supplementary inhalation anesthesia. This became rarer after the technique of Sise was generally acquired. For success all the precautions recommended by him have to be observed. None of the deaths can be counted as an anesthetic death. One case of fatal pneumonia occurred after a gas-oxygen-ether anesthesia. Fortunately gynecologists are not troubled by the pulmonary complications that make life so unpleasant for those who do gastric resections and splenectomy frequently.

Tables VI to VIII give the causes of death following the two operations. They are essentially the same for both, peritonitis, pulmonary embolism, and hemorrhage. In these latitudes where streptococcal infections are rare, where almost no erysipelas, etc., are seen, it is probable that many of the deaths due to peritonitis are secondary to some technical catastrophe. Here the staphylococcus is the predominating organism in wound sepsis and puerperal sepsis. Only one death was due to a true streptococcus peritonitis. Pulmonary embolism probably falls into the category of an unavoidable accident a little more easily than peritonitis. It has become an almost routine procedure to keep the patients in slight Trendelenburg position twenty-four hours after operation to prevent stagnation of blood in the pelvic veins and to maintain their collapse by gravity. Fatal hemorrhage occurred four times in the supravaginal group and twice in the total.

One of the latter patients deserves special mention. A 30-year-old colored patient had a simple total hysterectomy, bilateral salpingo-oophorectomy and appendectomy

TABLE VI. SUPRAVAGINAL. DEATHS AMONG WHITES

CAUSE OF DEATH	CAUSE OF OPERATION	AUTOPSY
1. Generalized peritonitis (Note: Intestine sutured to abdominal wall)	Tuboovarian abscess	Yes
2. Generalized peritonitis	Myoma and luteal cyst	No
3. Generalized peritonitis	Myoma	No
4. Acute strep. pelvic peritonitis	Myoma	Yes
5. Pulmonary embolus	Chronic nephritis. Pregnancy	Yes
6. Pulmonary embolus	Adenomyoma, endometrial polyp	Yes
7. Pulmonary embolus	Myoma, adenocarcinoma of fundus	Yes
8. Coronary thrombosis. (Note: Rt. ureter perforated)	Granulosal cell tumor of ovary	Yes
9. Sup. Mesenteric thrombosis. (Note: Avulsion of wound simultaneously)	Carcinoma of cervix, pregnancy	Yes
10. Secondary hemorrhage, uterine artery (5 hr. postoperative)	Previous operation (normal tissue)	No Abdomen re-opened
11. Secondary hemorrhage broad ligament	Previous operation (normal tissue)	No Abdomen re-opened
12. Volvulus 8 days postoperative. (Note: Avulsion of wound)	Two previous operations (corp. lut. hematoma)	No Abdomen re-opened
13. "Adynamic ileus"	Myoma. Chronic salpingitis	No
14. Intestinal obstruction 6 days postoperative	Flowing. Previous operation (normal tissue)	Yes
15. Pelvic peritonitis broncho-pneumonia	Myoma. Chronic salpingitis	Yes
16. <i>B. welchii</i> sepsis	Hydatidiform mole	Yes

under pontocaine anesthesia for chronic salpingitis. There was slight separation of the vaginal vault and she was kept in the house nineteen days after operation to receive astringent douches. Twenty-four days after operation she was admitted having a furious hemorrhage from the left uterine artery. This was fatal and autopsy revealed necrosis and infection in the pelvic floor with perforation of the left uterine artery. Trauma was suspected but never conclusively demonstrated. There is no question that the vaginal vault after total hysterectomy is a point of lessened resistance to infection and hemorrhage. There was only one immediately fatal case of obstruction following operation and that patient, the victim of a previous piecemeal operation, had received supravaginal hysterectomy for bleeding and died six days afterward unoperated.

The different causes of death for the two procedures were relatively as follows:

	SUPRAVAGINAL	TOTAL
Peritonitis	40 per cent	27 per cent
Pulmonary embolism	16	9
Hemorrhage	8	18

These statistics must be interpreted carefully because of the small series of total hysterectomies and because supravaginal hysterectomies have been performed on the sickest patients. Possibly the indication of added danger from hemorrhage from the vault is correct in the case of total hysterectomy.

As to morbidity, the usual criteria of temperature elevation is not a valid means of determining it. There is tremendous individual variation in capacity to reaction. Most colored patients had a sharper temperature

reaction than the white. Most patients who had had a total hysterectomy ran a low-grade temperature longer than those who had had supravaginal. This was undoubtedly because of the necessarily greater spill of blood and ooze, particularly from the posterior vaginal cuff and because of the portal that the open vaginal vault affords for sepsis. In this study only those nonfatal complications that damaged the patient or prolonged her stay were considered.

Operative accidents occurred in 1.3 per cent of those patients receiving total hysterectomy and 0.5 per cent of those receiving supravaginal hysterectomy. The reason for this was the occasional greater technical difficulty in freeing the cervix and vagina from the bladder in the total procedure. The only time the ureter was damaged in the performance of supravaginal hysterectomy was in the course of removing adnexal masses. Avulsion of the abdominal wound was most common in the colored group who received supravaginal hysterectomy, 0.5 per cent. The white

TABLE VII. SUPRAVAGINAL HYSTERECTOMY DEATHS AMONG COLORED

CAUSE OF DEATH	CAUSE OF OPERATION	AUTOPSY
1. Avulsion of wound, pelvic peritonitis, obstruction	Myoma	Yes
2. Generalized peritonitis	Myoma with necrosis and infection	No
3. Generalized peritonitis	Large myoma and carcinoma of the cervix	Yes
4. Generalized peritonitis operative wound of ileum	Large myoma. Tuberculous salpingitis	No
5. Pelvic peritonitis	Myoma. Tuboovarian abscess	Yes
6. Pelvic peritonitis	Achondroplastic dwarf in labor 48 hours	Yes
7. Generalized peritonitis	Tuboovarian abscess	No
8. Generalized peritonitis	Large myoma	Yes
9. Operative wound of sigmoid generalized peritonitis	Myoma. Chronic salpingitis	Yes
10. Generalized peritonitis	Myoma. Previous operation	No
11. Operative perforation of sigmoid. Generalized peritonitis	Myoma. Ovarian abscess	Yes
12. Pelvic abscess, intestinal obstruction, bronchopneumonia	Myoma. Hydrosalpinx	Yes
13. Probably generalized peritonitis	Chronic salpingitis	No
14. Generalized peritonitis	Previous operation (flowing), normal tissue	No
15. Pulmonary embolism	Tuboovarian abscess	Yes
16. Pulmonary embolism (on table)	Myoma	Yes
17. Probably pulmonary embolism	Myoma	No
18. Emboli in pulmonary vessels, intra-abdominal hemorrhage pelvic peritonitis	Myoma, tuboovarian abscess	Yes
19. Intra-abdominal hemorrhage	Myoma. Carcinoma of the cervix	Yes
20. Shock and hemorrhage (on table)	Myoma, ovarian abscess	No
21. Bronchopneumonia (G.O.E.*)	Myoma, chronic salpingitis	Yes
22. Bronchopneumonia (spinal)	Myoma, chronic salpingitis	No
23. Operative perforation of uterus. Pulmonary infarct. Cardiac failure	Hypertension, pregnancy	Yes
24. Pulmonary edema. Cardiac failure.	Myoma. Chronic salpingitis	No
25. Pelvic peritonitis. Uremia	Ablatio placentae	Yes
26. Subarachnoid hemorrhage. Pulmonary infarct	Myoma	Yes

\*Gas-oxygen-ether anesthesia.

TABLE VIII. TOTAL HYSTERECTOMY DEATHS

NO.	CAUSE OF DEATH	CAUSE OF OPERATION	AUTOPSY
<i>White</i>			
1	Peritonitis	Prolapse	No
2	Peritonitis	Fibromyoma, appendiceal abscess	No
3	Pulmonary embolism	Flowing, normal tissue	No. Embolectomy
4	Primary hemorrhage	Adenocarcinoma	No
5	Intestinal catastrophe (bleeding from bowel)	Flowing, normal tissue	No
<i>Colored</i>			
1	Peritonitis	Fibromyoma. Tuboovarian abscess	Yes
2	Primary hemorrhage	Ruptured pregnant uterus	Yes
3	Secondary hemorrhage from left uterine artery 24 days postoperative	Chronic salpingitis	Yes
4	Avulsion of wound 5 days post-operative. Ileus	Chronic salpingitis	Yes
5	Mania, cause unknown	Fibromyoma. Chronic salpingitis	No
6	Renal and cardiac failure	Fibromyoma	No

TABLE IX. NONFATAL COMPLICATIONS ASSOCIATED WITH SUPRAVAGINAL HYSTERECTOMY ON WHITE PATIENTS

Operative accidents: Cystotomy	1
Avulsion of the wound	1
Hemorrhage: {Secondary from broad ligament	1
{Secondary from the uterine artery	1
Thrombophlebitis	3
Intestinal obstruction	5*
Pelvic peritonitis	1
Pelvic cellulitis	1
Pelvic abscess	1
Wound sepsis	5
Pneumonia	3
Hematuria	1
Pyelitis	1
Cystitis	5
Draining sinus	1
Peripheral abscess	1
Carcinoma of the stump	1

\*Eight days, 9 days, 2 months, 5 months, 5 years, respectively.

group had 0.2 per cent for the supravaginal operation and 0.4 per cent for the total. Syphilis and diabetes were in no instance implicated. Low-grade sepsis was usually present, and there was an absence of fibroblastic response in the wound edges. Perhaps these patients were the opposites of those that obstruct and respond to low-grade sepsis by exuberant fibroblastic development.

Hemorrhage in the supravaginal group occurred secondarily and required reopening of the abdomen in two white patients. Once it was from the broad ligament as a whole and once from the uterine artery. In the total group there were four hemorrhages, all from the vaginal vault. Packing in one of these patients left her ultimately with a vaginal and abdominal fecal fistula. Four patients were delayed by failure of the vaginal vault to heal.

The true statistics on intestinal obstruction in the two groups cannot be given because of the paucity of follow-up examinations. All that can be said is that there were 15 known cases in the supravaginal group and 4 in the total group. Most of these occurred in colored patients. The longest interval following operation was five years. This is an incidence of intestinal obstruction of about 1 per cent for each type of operation, but no great significance can be attached. The other complications were about the same for each group.

TABLE X. NONFATAL COMPLICATIONS ASSOCIATED WITH SUPRAVAGINAL HYSTERECTOMY ON COLORED PATIENTS

Operative accidents	{ Cystotomy	4
	{ Intraligamentous myoma left behind	1
	{ Ligation of ureter	1
Avulsion of the wound		4
Shock		5
Hemorrhage: Secondary from wound		1
Thrombophlebitis		7
Intestinal obstruction*		10
Fecal fistula		1
Pelvic cellulitis		5
Pelvic abscess		2
Wound sepsis		32
Pneumonia		5
Pyelitis		5
Hematuria		2
Cystitis		1
Hemorrhage from cervix		1
Acute appendicitis 4 years later		2
Hematoma of wound		2
Infusion into thorax		1
Persistent sinus		1
Paratyphoid		1
Psychosis		1
Carcinoma of the stump		2

\* Immediately postoperative 11 days, 1 month, 5 months, 10 months, 1 year, 1 year (fatal), 1 year, 9 months (due to retained Meckel's diverticulum), 4 years, 5 years.

TABLE XI. NONFATAL COMPLICATIONS ASSOCIATED WITH TOTAL HYSTERECTOMY ON WHITE PATIENTS

Operative accidents	{ Cystotomy	3
	{ Laceration of transverse colon	1
Avulsion of wound (one only to fascia)		2
Shock		2
Hemorrhage from vaginal vault		1
Thrombophlebitis		3
Intestinal obstruction		1 (1 month)
Pelvic abscess		1
Pelvic cellulitis		1
Bronchitis		1
Hematuria		1
Cystitis		1
Pyelitis		1
Hematoma of the wound		2
Gastric distention		1
Parotitis		1
Radial palsy		1
Brachial palsy		1
Failure of vaginal vault to close		4



TABLE XII. NONFATAL COMPLICATIONS ASSOCIATED WITH TOTAL HYSTERECTOMY ON COLORED PATIENTS

Operative accidents: Division of ureter	1
Shock	1
Hemorrhage from vaginal vault	3*
Intestinal obstruction	4†
Pelvic peritonitis	1
Pelvic abscess	3
Pelvic cellulitis	1
Wound sepsis	1
Pulmonary infarct	1
Pyelitis	1
Hematoma of wound	1

\*One later developed abdominal and vaginal fecal fistulas.

†One month, twice, 5 and 11 months, 1 year and 6 months (fatal).

Three cases of carcinoma of the stump were found to have developed in patients who received supravaginal hysterectomy. This is admitted with reluctance, because only about 25 per cent of the patients have been adequately checked by follow-up examinations. The rural population and the prevalence of illiteracy were responsible. Therefore, the incidence of carcinoma of the stump in this series will later be found to be higher.

During this period, 35 patients with carcinoma of the cervical stump were seen in Duke Hospital.<sup>1</sup> Comparing this number with the 1,243 supravaginal hysterectomies performed simultaneously, as Meigs<sup>4</sup> did with the Massachusetts General Hospital series, the dubious figure of 2.8 per cent is obtained. This must be interpreted with utmost caution, because the number of hospitals in which surgery is done in this locality is large and the number of those with radiologic facilities is small. Therefore, there is a great opportunity for the nonlucrative patients with malignancy to be concentrated and the lucrative patients with surgical complaints to be scattered and treated locally.

### CONCLUSIONS

It must be pointed out that no surgical procedure is without danger. Any surgical therapeutic measure is a double-edged sword and may kill as well as cure. In this clinic, the gross mortality of a small series of patients receiving total hysterectomy and a large series receiving supravaginal were essentially the same, viz., 2.9 and 3.4 per cent, respectively. This must be critically interpreted, because the less radical procedure was reserved for the poorer risks. With well-trained gynecologists the mortality for the two procedures ought to approach the same figure. Inadequately trained individuals can more safely perform the more conservative operation. In the main, it is not the operation so much as the condition demanding operation that raises the mortality rate. The vaginal vault following total hysterectomy is like the placental site of the puerperal uterus, a point of lessened resistance. Like the placental site, it is likely to bleed and become infected, and it is much closer to the peritoneum. Therefore, no gynecologist should reflexly do a total hysterectomy or a supravaginal hysterectomy. He should rather run through the prudential algebra recommended by Benjamin Franklin and decide whether the risk of excising the cervix is justified. Only by evaluating such factors as the severity of the intra-abdominal proce-

ture, the obesity of the patient, the amount of prolapse, and the condition of the cervix can he elect the proper procedure. If the cervix can be removed easily, it should be done, but supravaginal hysterectomy should by no means be abandoned.

#### REFERENCES

- (1) *Pearse, R. L.*: North Carolina M. J. 1: 534, 1940. (2) *Dupertuis, S. M., and Zollinger, R.*: Surg., Gynec. & Obst. 67: 689, 1938. (3) *Sise, Lincoln F.*: S. Clin. North America 15: 1501, 1935. (4) *Meigs, J. V.*: AM. J. OBST. & GYNEC. 31: 358, 1936.

### A STUDY OF ONE HUNDRED AND FIFTY CONSECUTIVE CASES OF ECTOPIC PREGNANCY\*

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THIS report comprises a study of 150 consecutive ectopic pregnancies of less than twenty-eight weeks' duration. They occurred in the service of the Medical College of Virginia Hospitals during the ten years from Jan. 1, 1930, through 1939. This is an incidence of 1.46 per cent of the total obstetric admissions.

During the same period, there were ten extrauterine pregnancies of more than twenty-eight weeks' duration. The late extrauterine pregnancies present a different problem, and will be reported in another paper.<sup>1-4</sup>

The Medical College Hospitals serve not only Richmond but a large industrial and rural territory from which only abnormal cases are usually hospitalized. Therefore, the high incidence of ectopic gestation reported by us cannot be considered the average for Richmond.

In our patients it seems probable that endocrine dysfunction deserves more study as a cause of relative or temporary sterility than salpingitis. Twenty-six per cent of the women had previously aborted and 20 per cent had been sterile five years or more. Definite evidence of salpingitis was found in 22 per cent, and only 2 patients had previously been operated upon for ectopic pregnancy.

#### ANALYSIS OF MATERIAL

There were 59 white and 91 negro women. From the operative notes there were 2 ovarian pregnancies and 1 interstitial pregnancy. Some of the records failed to state the location of the rupture in the tube, and no classification of this type was attempted. Most of the women were admitted after the tube had ruptured. Often the patient had been sick two or three weeks, and pelvic inflammatory disease was frequently the complication that had to be ruled out after hospitalization.

Forty per cent of the patients presented no particular diagnostic problem, and were operated upon within twenty-four hours after admission. An additional 13 per cent were operated upon within the next twenty-four hours. Appendicitis was

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the original diagnosis in 8 patients. In almost 50 per cent of the other patients, the primary or second diagnosis was old pelvic inflammatory disease. Six per cent of the patients were in the hospital three weeks or more before operation.

A positive diagnosis of an early unruptured ectopic gestation is difficult to make. The patient with a recently ruptured tube, and the typical picture of internal hemorrhage, rapid pulse, increasing leucocytosis, decrease in red blood cells and hemoglobin usually offers no great diagnostic problem, and immediate operation is indicated. In the neglected case with symptoms of several weeks' duration, the differential diagnosis is a real problem, and a study of our cases gives some information that may be of value.

TABLE I. AGE

Total Number of Cases 150; White 59, or 39.33 per cent; Negro 91, or 60.66 per cent

AGE (YEARS)	PATIENTS (NUMBER)	PER CENT
Under 20	13	8.66
20 to 25	38	25.33
25 to 30	47	31.33
30 to 35	30	20.00
35 to 40	19	12.66
40 or over	3	2.00

Table I shows that 76.66 per cent of the patients were between the ages of twenty and thirty years. Only 8.66 per cent of the women were less than twenty years old and 14.66 per cent were more than thirty-five years old. The ratio of white to negro patients was about the same as that found in the total admissions.

TABLE II. MENSES

	NUMBER PATIENTS	PER CENT
No amenorrhea	76	50.66
Missed one menstrual period	42	28.00
Missed two menstrual periods	25	16.66
Missed more than two menstrual periods	3	2.00

The importance of an accurate menstrual history may be seen in Table II. Seventy-six patients denied any amenorrhea, but a careful analysis of the histories of these women shows that frequently the menses had been delayed, scant, or irregular. Seventy-eight per cent of the patients had menstruated regularly or missed only one menstrual period. Only 2 per cent of the group had missed more than 2 menstrual periods.

TABLE III. VAGINAL BLEEDING

	NUMBER PATIENTS	PER CENT
Abnormal menstrual periods	40	26.66
Spotting	18	12.00
Intermittent bleeding	79	52.66
Continuous slight bleeding	21	14.00
Profuse	7	4.66
No bleeding	39	26.00

The difficulty one encounters in correctly classifying vaginal bleeding in the presence of ectopic gestation may be seen in Table III. Seventy-four per cent of the patients had vaginal bleeding, usually scant, but 11 per cent gave a history of having passed small clots 1 cm. or less in diameter.

Table IV shows that 72 per cent of the patients complained of cramplike pain, and 82 per cent had either cramplike or dull aching pelvic pain. The classic history of sharp pain and fainting was obtained in only 17 per cent of the women. Low abdominal or pelvic tenderness was noted in 122 patients, 80 per cent. Severe pelvic tenderness was observed in 48 patients. A pelvic mass was palpated in approximately two-thirds of the patients.

TABLE IV. PAIN

	NUMBER PATIENTS	PER CENT
None	2	1.33
Shoulder pain	3	2.00
Dull ache	16	10.66
Cramp	108	72.00
Sharp with fainting	26	17.00
Sharp without fainting	47	31.33

TABLE V. TEMPERATURE (ADMISSION)

	NUMBER PATIENTS	PER CENT
Below 99	39	26.00
99 to 100	44	29.33
100 to 101	43	28.66
101 to 102	21	14.00
102 to 103	3	2.00

In Table V the temperature was below 100° F. in 55 per cent of the women, and below 101° F. in 84 per cent of all the patients. It is interesting to note that the temperature was 102° F. or above in only 2 per cent of the cases.

TABLE VI. BLOOD PRESSURE SYSTOLIC (ADMISSION)

	NUMBER PATIENTS	PER CENT
Below 70	6	4.00
70 to 80	8	5.33
80 to 90	6	4.00
90 to 100	11	7.33
100 to 110	24	16.00
110 or above	81	54.00
Not recorded	14	

The admission blood pressure is shown in Table VI. In only 36 per cent was the systolic pressure below 110. Twenty per cent of the patients were in shock when admitted.

TABLE VII. PULSE RATE (ADMISSION)

	NUMBER PATIENTS	PER CENT
Below 80	4	2.66
80 to 90	46	30.66
90 to 100	33	22.00
100 to 110	34	22.66
110 to 120	9	6.00
120 or above	24	16.00

In Table VII the pulse rate on admission was below 80 in less than 3 per cent of the patients, and between 80 and 110 in 74 per cent. This increase in pulse rate was greater than one would expect with the temperature and slight leucocytosis in this group of women.

TABLE VIII. WHITE BLOOD CELL COUNT (ADMISSION)

	NUMBER PATIENTS	PER CENT
Below 10,000	54	36.00
10,000 to 15,000	53	35.33
15,000 to 20,000	26	17.33
20,000 or above	13	8.66
Not stated	4	2.66

Thirty-six per cent (Table VIII) of the patients had a leucocyte count below 10,000, and 71 per cent below 15,000. The leucocyte count increases in the presence of intraperitoneal hemorrhage, but apparently subsides rapidly after hemorrhage stops. In salpingitis or infection secondary to abortion, the white cell count remains elevated or decreases slowly.

TABLE IX. RED BLOOD CELL COUNT (ADMISSION)

	NUMBER PATIENTS	PER CENT
Below 2 million	11	7.33
2 to 3 million	43	28.66
3 to 4 million	47	31.33
Above 4 million	31	20.66
Not stated	18	12.00

The red cell count on admission was below two million in only 7 per cent of the patients as shown in Table IX. In this group the rupture had been recent and the hemorrhage severe. The erythrocyte count was three million or above in 51 per cent of the patients.

TABLE X. HEMOGLOBIN (ADMISSION)

	NUMBER PATIENTS	PER CENT
Below 50 per cent	29	19.33
50 to 60 per cent	28	18.66
60 to 70 per cent	27	18.00
70 to 80 per cent	30	20.00
80 per cent or above	29	19.33
Not stated	7	4.66

Table X shows the hemoglobin was below 50 in 19 per cent of the patients. A rapid decrease in hemoglobin is often more important than the initial reading. When this decrease is associated with a rapid drop in red cell count and increase in leucocytes, it is very suggestive of internal hemorrhage.

TABLE XI. CONDITION OF PREGNANCY AT TIME OF OPERATION OR AUTOPSY

	NUMBER PATIENTS	PER CENT
Tube ruptured	136	80.66
Free blood in peritoneal cavity	97	64.66

Table XI shows that the patient with an ectopic pregnancy seldom seeks medical care unless she has pain or some discomfort. The presence of these symptoms indicates extravasation of blood into the peritoneal cavity or a ruptured ectopic in 9 out of 10 cases.

TABLE XII. DIFFERENTIAL DIAGNOSIS, PREOPERATIVE

	NUMBER PATIENTS	PER CENT
Pelvic inflammatory disease	50	33.33
Tuboovarian abscess	37	24.66
Ovarian cyst	20	13.33
Appendicitis	8	5.33

A positive diagnosis of ectopic pregnancy was easily made before operation in 40 per cent of the patients. In 60 per cent the preoperative diagnosis was questionable and the other diagnoses recorded either alone or with ectopic gestation are shown in Table XII. Evidence of pelvic inflammatory disease was found in 34 patients, 22.66 per cent.

TABLE XIII. TRANSFUSION

	NUMBER PATIENTS	PER CENT
500 c.c. whole blood (citrate 11, multiple syringe 33)	44	29.33
1,000 c.c. or more whole blood (citrate 2, multiple syringe 16)	18	12.00
Auto transfusion	1	0.66

Table XIII shows that 40 per cent of the patients were transfused. The method used for each patient is stated, but the figures do not indicate the total number of transfusions.

## COMMENT

The mortality rate in this study is high. Twelve patients, or 8 per cent, died. Four women died before operation, and correcting for these, the operative mortality rate is 5.4 per cent. Most of the patients were on the hospital wards, and all of the deaths occurred in this group.

It is of interest to note that two patients died on the operating table before operation, and just before a transfusion was ready. This indicates that it is unwise to delay operation until the patient is out of shock. Another patient died before a donor could be obtained. The fourth woman died from pelvic cellulitis, but at autopsy an old ruptured ectopic pregnancy was found. If the diagnosis is ruptured ectopic pregnancy, immediate laparotomy and removal of the pregnant tube is indicated. Transfusion and other measures to combat shock should be carried out during the operation.

Eight women died after operation. Three of these deaths resulted directly from hemorrhage and shock. These patients were given transfusions of whole blood, but they were in such poor condition that they failed to respond. One death was due to thrombosis of the femoral veins and atelectasis. Another death was due to arsphenamine poisoning.

Three other deaths resulted from peritonitis, and in 2 of these, the operation was for peritonitis and not ectopic gestation.

## SUMMARY AND CONCLUSIONS

1. One hundred and fifty cases of ectopic pregnancy have been reported, with a mortality rate of 8 per cent. This could be reduced to an operative mortality of 5.41 per cent by eliminating four patients who died before operation.

2. A complete and accurate history is most valuable in arriving at a correct and early diagnosis. The menstrual history is particularly important, and often the patient states that her last period was delayed, scant, prolonged, or abnormal. Careful inquiry will reveal a period of amenorrhea, that is, a cycle of more than twenty-eight days before the vaginal bleeding was noticed.

3. A dull ache or cramplike low abdominal or pelvic pain was recorded in 82 per cent of the patients.

4. A typical history with sudden pain, syncope, and shock was obtained from only 26 of the patients, 17 per cent.

5. Thirty-one patients, 20.66 per cent, had been sterile five years or more.

6. Thirty-nine patients, 26 per cent, gave a history of one or more abortions.

7. The temperature usually shows slight elevation, rarely above 100° F. It was below 99° F. in 39, or 26 per cent, and below 100° F. in 83, or 71 per cent, of the patients.

8. A decrease in hemoglobin and red blood cell count, associated with recurring pelvic pain and temporary leucocytosis was frequently observed. The leucocyte count was below 10,000 in 54, or 36 per cent, and above 15,000 in only 25 per cent of the patients.

9. The sedimentation rate was of value when pelvic inflammatory disease was suspected. A rapid rate is seldom seen unless infection is present. Massive hemorrhage may occasionally increase the rate.

10. Manipulation of the cervix usually causes excruciating pain in the presence of ectopic gestation.

11. Posterior colpotomy is seldom necessary.

12. Pelvic examination must be gentle.

13. Fifty per cent of the deaths could probably have been prevented if the women had consulted a physician and entered the hospital at the onset of symptoms.

14. Immediate operation, transfusion with whole blood, and other supportive measures, give the best results.

#### REFERENCES

- (1) *Ware, H. H., Jr., and Main, R. J.*: AM. J. OBST. & GYNEC. 27: 756, 1934.  
 (2) *Ware, H. H., Jr.*: South. M. J. 27: 540, 1934. (3) *Idem*: New York State J. Med. 36: 153, 1937. (4) *Ware, H. H., Jr., and Main, R. J.*: J. A. M. A. 111: 524, 1938.

### PLACENTA BILOBATA\*

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PLACENTA BILOBATA is one of a series of variations in placentation which has great practical significance, yet has received little study. In an extended investigation of the form of all placentas delivered at the University of Georgia School of Medicine, 355 bilobate placentas have been recovered.

An analysis of correlated facts now seems to indicate the major causal factors of the condition and these, for the most part, do not support previous theories bearing on the subject.

#### HISTORICAL REVIEW

Walder<sup>1</sup> reported one case in which one lobe was on the anterior wall and the other on the posterior wall of the uterus. He explained the condition as due to pathology of the mucosa from old inflammation with endometrium inadequate for production of a discoid placenta and the resulting spread of chorionic invasion to other parts. He admits no proof of the idea.

Podleschka<sup>2</sup> offers a rather complicated classification of the rarer-shaped human placentas. He reported the cases of a very rare type which he called placenta duplex, only one or two of which we have seen. There were no history or signs of preceding inflammatory processes in regard to his specimen, which consisted of two completely separated discoid placentas with a bridge of membranes between, measuring 7.5 cm. at the narrowest place, the cord inserting into the membrane bridge between. He also described a case with two lobes of nearly equal size but connected by a bridge of tissue. He did not give the intrauterine site of the various portions. He stated that Ahfeld thought that one portion was located on the anterior and the other on the posterior wall, and that Gott-

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shalk assumed that these resulted from nidation of the ovum in the lateral border of the uterus with development of the placenta on both anterior and posterior walls. He declares that Ribemont-Dessaignes considered the condition as evidence of atavism, in that the placenta on both walls approached the type found in certain monkeys. He states that Bumm<sup>3</sup> and Schiffman<sup>21</sup> assumed double nidation in their cases. He also states that Lahm<sup>4</sup> disagrees with these ideas in that his study of pregnancy at the third month always revealed a discoid placenta. Podleschka's own view approximates that of Walder in that he thinks the anomaly of placental shape results from nutrient variations in the endometrium in its adaptability for chorionic invasion. He also hints that the villi located in the decidua capsularis may grow on through and invade the opposite wall.

Itzkin<sup>5</sup> described a bilobate placenta of nearly equal lobes, one on the anterior and one on the posterior uterine wall. He also described one similar to the duplex placenta of Podleschka. In his case there was a 7 cm. bridge of membranes between



Fig. 1.—Typical bilobate placenta of equal lobes, one lobe from the anterior and one from the posterior uterine wall. The line of demarcation lay over the lateral sulcus of the uterus which separates the two walls. The cord insertion is typical in that it was inserted into the region of the demarcation.

the two discoid portions 15 and 20 cm. in diameter, respectively, the cord having inserted into the larger of the two. The bridge was over the fundal sulcus or fissure, and the two disks lay one on the anterior wall and one on the posterior wall of the uterus. Itzkin rejects both the mechanical and the atavism theory in favor of the inadequate decidua theory, and maintains that poor decidua compels the chorionic villi to spread to other parts.

Roest<sup>6</sup> reported the case of a bilobate placenta of nearly equal lobes. However, in his case, the cord inserted probably on the opposite side of the uterus inasmuch as the velamentous insertion was 14 cm. from one and 15 cm. from the other lobe. He gave no intrauterine position of the two lobes.

Levy<sup>7</sup> reported the history of a case of dystocia due to bilobate placenta located in the lower uterine segment, one lobe of which apparently prematurely separated and blocked the birth canal.



## DESCRIPTION OF MATERIAL

The term bilobate is used, because in almost all of the extra-lobed placentas, there is usually only one accessory lobe in addition to that of the primary placenta (Fig. 1) to which most frequently the cord is attached, although in a few cases there may be two or more extra lobes. In most instances the extra lobe (Fig. 3, 1191) is very small in comparison with the main portion of the placenta which is usually discoid shaped. In some cases the extra lobe equals in size the primary placenta (Fig. 3, 1735), but in most cases the extra lobe is sessile to or connected to the primary placenta by a narrow neck of placental tissue in the chorion. In some specimens the lobes are separated by membranes through which run the fetal blood vessels supplying the extra lobe or lobes, and in these the condition is known

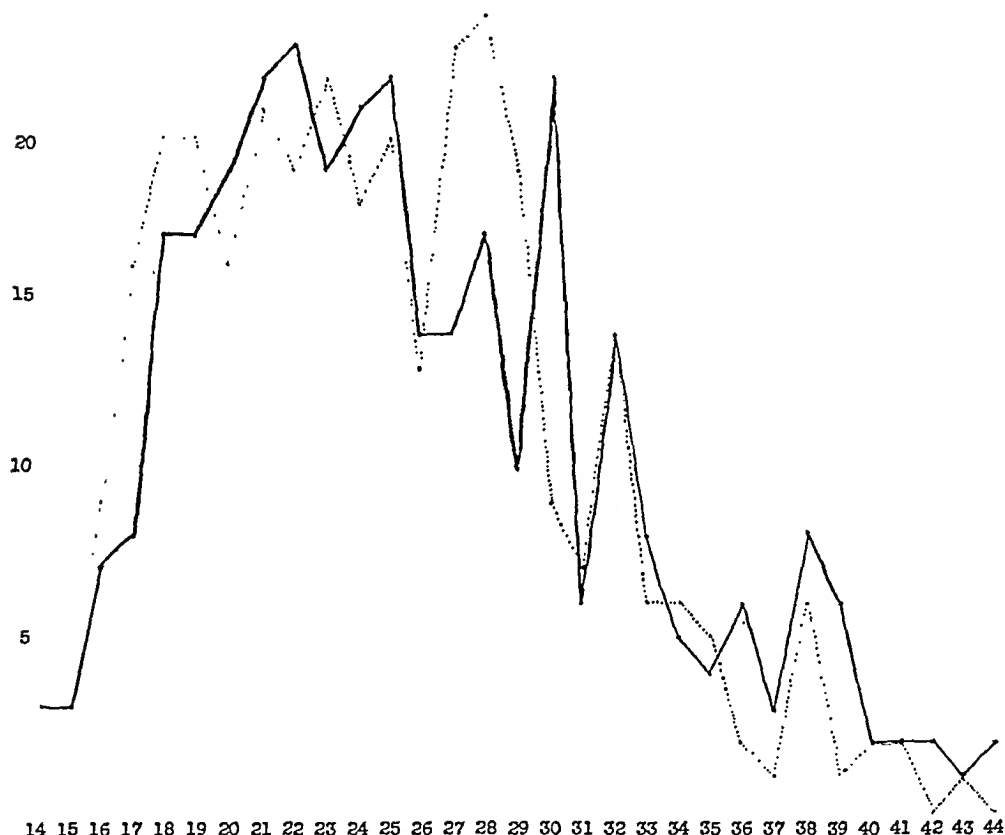


Fig. 2.—The age incidence curve of bilobate placentas is given by the continuous line. The broken line gives the age incidence in a similar group. The horizontal numbers represent the age of the patients. The vertical numbers represent the incidence in each age group.

as placenta succenturiate (Fig. 3, 2381). In 3 of our cases there were single succenturiate lobes, usually small, and in 3 others there were two succenturiate lobes with each placenta. A tabulation of the 389 extra-lobed placentas, including a few not in this study, revealed a single extra small lobe 4 or 5 cm. in diameter sessile to or connected to the placenta by a narrow neck of placental tissue in 166 cases (42.5 per cent). The extra lobe had an area of about one-third or one-half of that of the primary placenta in 123 cases (31.5 per cent), and there were 84 placentas with two essentially equal lobes, 21.5 per cent. In 16 cases (4 per cent), there were two extra lobes (Fig. 3, 2009).

The margin of the placenta deserves some attention as to whether it is normal, marginate, or circumvallate, and a record was made in each case as shown in the outline drawings. Placentas with normal edge were recorded in 250 cases. There was margination with a narrow white necrotic band on the fetal surface at the

circumference in 105 placentas (Fig. 3, 1332). This, as a rule, occurred in the larger lobe and generally on the side opposite to the small lobe. In 7 cases the marginate band of necrosis appeared in the small lobe only, and in 5 cases it appeared in both lobes. The margination appeared in one-eighth of the circumference of some placentas; in others it appeared in more of the circumference, and in 18 placentas the whole edge of the larger lobe was marginate.

#### STUDY BY FETAL SAC DISTENTION METHOD

A study of these placentas was made by a technique formerly described by the senior author.<sup>8, 9</sup> For convenience the method may be given here:

"If care is exercised in delivering the placenta it is possible to obtain the placenta and fetal membranes quite intact so that the sac is complete with the exception of the opening over the cervical area through which the fetus emerged at birth. Now by the simple procedure of submerging this sac in a tank of water up to the cervical rupture and then introducing into the cavity of the sac a known quantity of water to fill and distend it to its capacity, it is found that the sac assumes the exact shape of the distended uterus from which it came. The sac takes on a rough pyriform shape and, most remarkable of all, in most cases it develops more or less pointed bulges opposite each other at the widest part and farthest from the cervical tear. Without a doubt these correspond to the areas over which the tubes arise. This assumption is furthered by the fact that several unopened pregnant uteri, hardened in formalin, when bisected revealed the identical bulges over these areas."

There were 131 of these bilobate placentas with membranes intact enough for study by this method, from labors at term, and 16 from abortions or premature labors. Clay models made to scale were constructed for each of these, and the placenta was depicted thereon. These are illustrated in Figs. 3 and 4. The outline of the uterus appears in each case as an anterior or posterior surface view. The cervical end is readily recognized and is apparent in most cases. It will be noted that in the great majority of cases the secondary placental lobe extends across the lateral sulcus, separating the anterior and posterior flat surfaces. This point is illustrated by drawing the extra lobe as though it were lifted off of the opposite wall and extended out into space. This suggests that extension of placental tissue over this sulcus results in bilobation, but tabulation revealed that quite as many placentas lay across the sulcus at the apex of the fundus as across the two side sulci combined.

#### THE POSITION OF INSERTION OF THE UMBILICAL CORD

The umbilical cord was inserted into the center of the major (primary) lobe in about 50 per cent of the cases, into the major lobe eccentrically in 18 per cent, and into or near the line dividing the two lobes in 30 per cent. In about 2 per cent there was velamentous insertion. It should be noted that the third type of cord insertion is more common if the lobes are nearly equal.

#### PLACENTAL THICKNESS

These placentas were studied by obtaining the index weight in grams divided by the area in square centimeters (Table I). This gives approximately the average thickness in centimeters. The weight was that of the superficially washed placenta, fetal membranes, and cord. The area in square centimeters was obtained by determining the area enclosed in the outline of the placenta on a glass plate pressed firmly against the placenta on a plane surface. Similar pressure was exerted in each case so that comparable results were obtained. Table I shows that as a rule the greater the area of the lobate placenta, the less the thickness. The main exception was in the case of the placenta of the largest area of all which also weighed the most of any bilobate. This placenta, illustrated in Fig. 3 (No. 804), had an area of 552 sq. cm. and weighed 1,039 Gm. It covered almost all of both anterior

FULL TERM PREGNANCY SACS

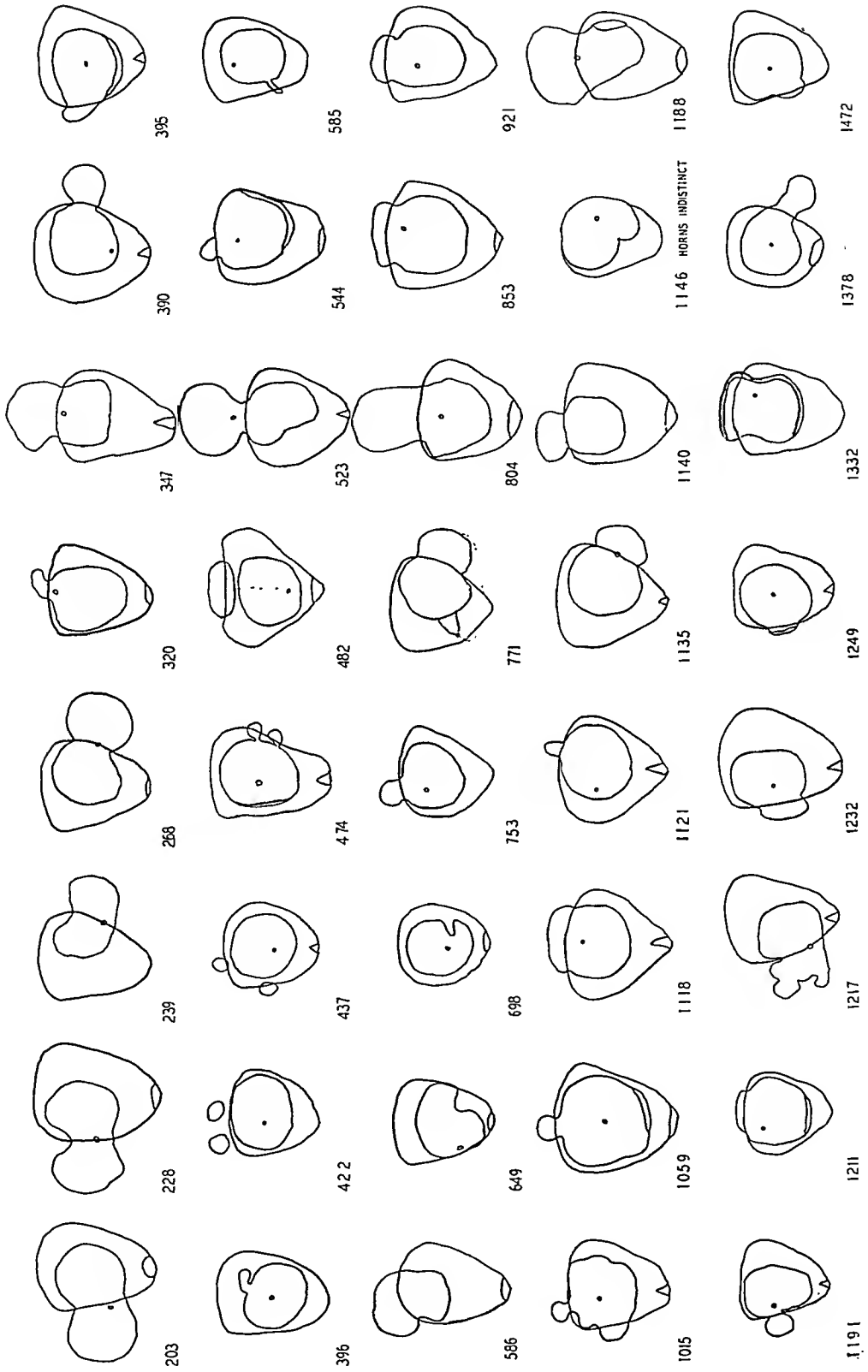


Fig. 3.

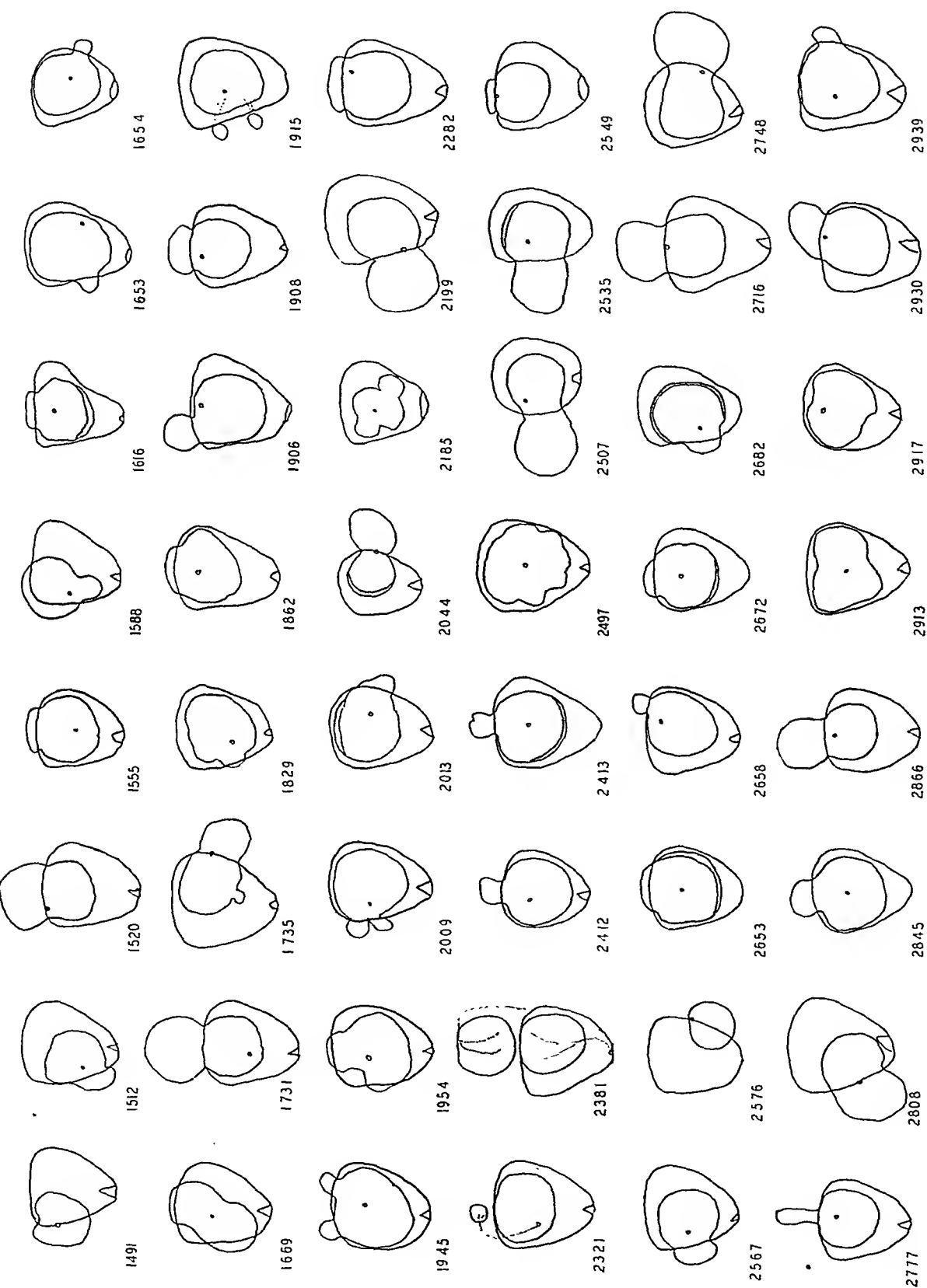


Fig. 3—Cont'd.

## FULL TERM PREGNANCY SACS - CONT.

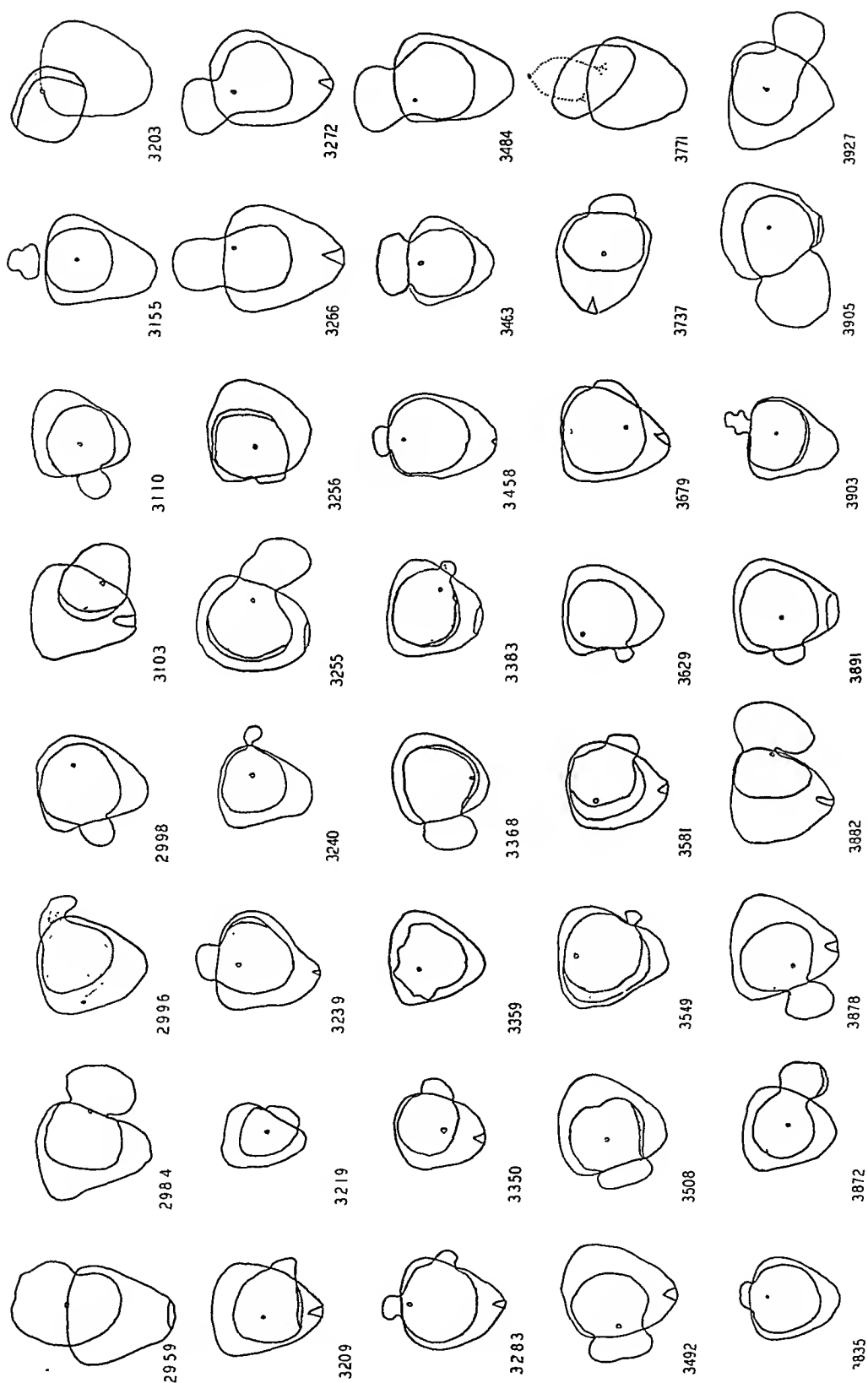
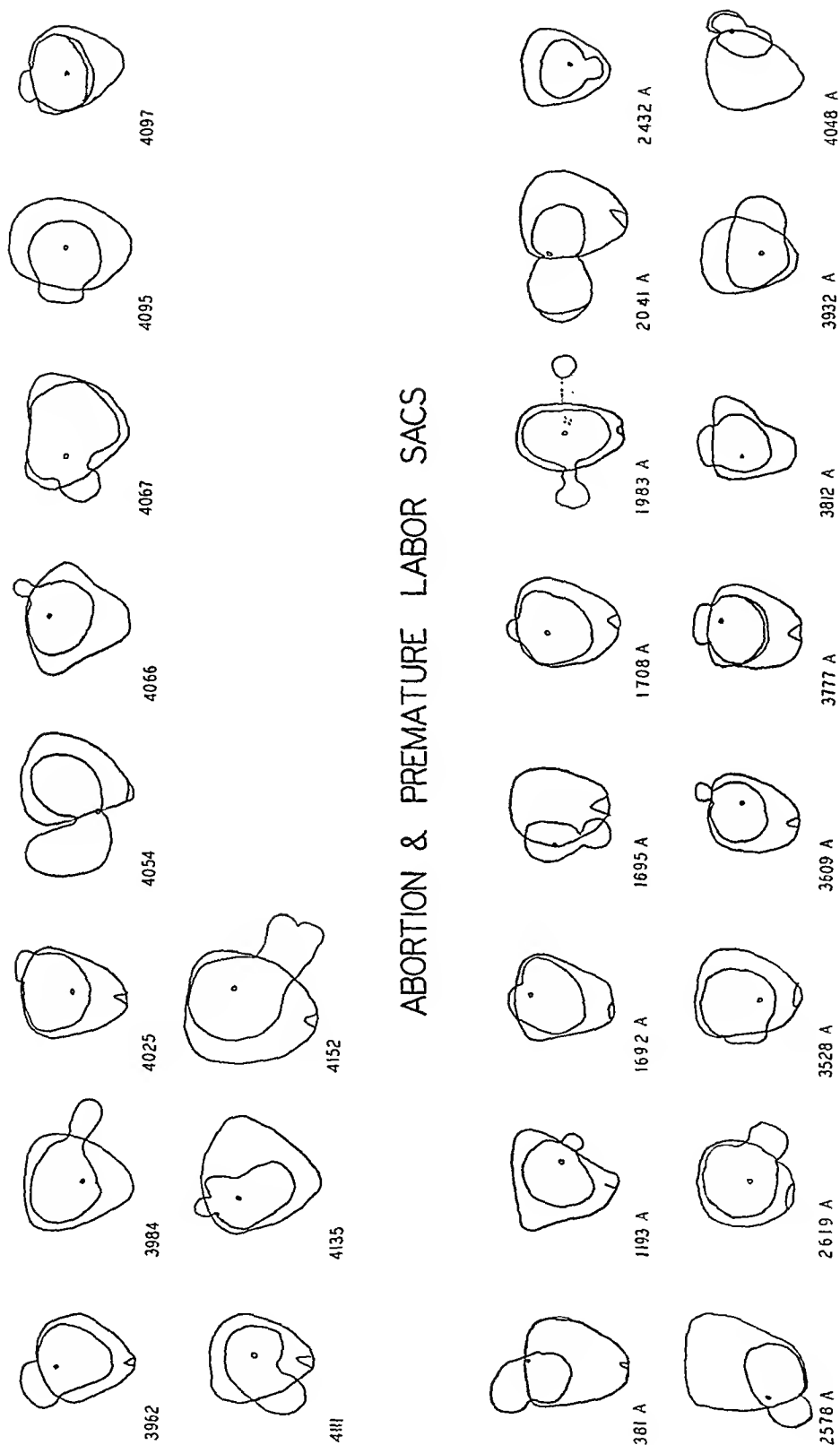


FIG. 4.



ABORTION & PREMATURE LABOR SACS

Fig. 4—Cont'd.

and posterior walls, and the two lobes connected over the fundal apex. The infant in this case weighed  $8\frac{1}{2}$  pounds at birth, and there was no hydramnios. The placenta covered about 45 per cent of the area of the fetal sac. The average placental coverage at term in all types is about 25 per cent.

TABLE I. SHOWING FREQUENCY RELATION OF SURFACE AREA AND THICKNESS IN 127 MATURE LOBATE PLACENTAS

AREA IN SQUARE CENTIMETERS							
200-250	250-300	300-350	350-400	400-450	450-500	500-550	550-600
1.66	1.26	1.47	1.85	1.33	1.49	1.49	1.88
2.38	1.72	1.76	1.58	1.72	1.86	1.32	
1.60	1.79	1.97	1.75	1.78	0.36	1.47	
1.69	1.66	1.76	1.51	1.91	1.41		
	1.64	1.51	1.40	1.52			
	1.79	1.49	1.77	1.57			
	2.21	2.21	1.81	1.50			
	2.31	1.48	1.50	0.92			
	2.09	2.26	1.83	1.48			
	1.54	1.26	1.66	1.75			
	1.79	1.76	1.78	1.25			
	1.24	1.39	1.75	1.94			
	1.70	1.89	1.54	1.73			
	1.56	1.98	1.83	1.42			
	1.64	1.70	1.48	1.42			
	1.63	1.58	1.77				
	1.43	1.30	1.62				
	2.01	1.45	1.60				
		1.54	2.20				
		1.52	1.65				
		1.48	1.62				
		1.24	1.67				
		1.87	1.67				
		1.26	1.32				
		1.58	1.49				
		1.60	1.78				
		1.84	1.41				
		1.67	1.95				
		1.72	1.11				
		1.53	1.83				
		1.71	1.76				
		1.67	1.89				
		1.65	1.46				
		2.12	2.07				
		1.59	1.37				
		1.64	1.73				
		2.03					
		1.92					
		1.74					
		1.48					
		1.86					
		1.62					
		1.52					
		1.51					
		1.95					
		2.32					
AVERAGE THICKNESS IN CENTIMETERS							
1.83	1.72	1.70	1.67	1.55	1.28	1.43	1.88

STATISTICAL TREATMENT OF DATA ON FREQUENCY, PREMATURITY,  
AGE AND RACE OF MOTHER

Among 4,098 placentas there were 355 bilobate placentas, 327 of which were full term and 28 from abortion or premature labors, with the fetus weighing less than 5

pounds. This is an incidence of 8.6 per cent, and this percentage holds good for full-time or abortion placentas. In this series, placental lobation occurred about 4 per cent more frequently in the white patients than it did in the negro patients. In the whole series of more than 4,000 pregnancies, there were 62.8 per cent white women and 37.2 per cent negro women. In the bilobate placental series there were 67 per cent white women and 33 per cent negro women.

The age incidence curve is given in Fig. 2 compared with the age incidence of all pregnancies in a similar group of patients.

Bilobation of the placenta was found in the 28 abortion or premature labor cases; 14 at the eighth month, 7 at the seventh month, 4 at the sixth month, 1 at the fifth month, and 2 at the third month.

#### DISCUSSION

The incidence of 8 per cent lobate placentas in our series indicates that this condition is far more common in human placentation and deserves much greater consideration than it has received. The identical incidence in premature labors shows that it is not per se a cause of abortion or early labor. The age group incidence is quite similar to that of pregnancy in general, and this speaks for a fortuitous etiology rather than an endometrial pathologic basis.

Our study shows quite definitely that implantation of the ovum must have taken place in or near a sulcus separating the two relatively flat surfaces of the anterior and posterior uterine walls, be this above or to the sides. Many of these specimens also bring up the question of depth of implantation into the decidua and the formation of a decidua capsularis. In regard to implantation we maintain the three following propositions: (1) Chorionic villi surrounding the implanting ovum will grow and thrive in any adequate decidual soil available on any side of the ovum. (2) Chorionic villi die and become necrotic if decidual nourishment fails or if the villi are pulled away from their original bed. (3) Villi once displaced cannot take root in other soil.

A consideration of the drawing of the individual fetal sacs and their placentas shows that most of them are located on both the anterior and posterior walls. Of these the vast majority are connected by placental tissue from lobe to lobe. In these the implantation must have been in the region of the sulcus or very near it and very superficially, so that chorionic villi implanted into the endometrium of the sulcus and likewise into that of both the flat surfaces, often more into one surface than into the other. In a few cases such as Fig. 3 (Nos. 482, 2381) and Fig. 4 (No. 3155), and in cases of Podleschka and of Itzkin there was a bridge of membranes between the two lobes (placenta duplex). Now it is possible that there was implantation in the sulcus here also with atrophy of the villi in the sulcus itself and persistence of villi in both the anterior and posterior uterine walls. However, it is much more plausible to consider that the implantation was near the sulcus, but so superficially as to implant into each wall. This is a common condition in certain monkeys which uniformly develop placenta duplex (macaque), one lobe on each wall. The only other plausible explanation is that the villi growing into the decidua capsularis then grow on through the surface, spanning the uterine cavity and into the adjacent decidua of the opposite uterine wall. According to Wislocki and Streeter,<sup>10</sup> in the macaque



there is marked thickening of the endometrial epithelium in the opposite wall directly over the implantation site, and after twelve days or so this is invaded by villi from the exposed abembryonic pole of the blastocyst. It will be interesting to ascertain whether anything similar occurs in the chimpanzee and in the human being. This study suggests that such may rarely occur in the human ovum implantation.

There are in addition several cases of irregular shaped placentas (Fig. 3, Nos. 2185, 2917, and Fig. 4, Nos. 3359, 2432 A) which are definitely limited to one wall, anteriorly or posteriorly. While in the extensive series, these are in the great minority, they must be explained on the basis of localized weak invasion, poor soil, atrophy and resorption of the villi due to premature separation, or infarction and necrosis of other cause.

Finally, there are a few instances in which implantation was directly in the sulcus separating the anterior and posterior walls, but the placenta in each case was discoid with little evidence of lobation (Fig. 3, No. 2576, and Fig. 4, Nos. 3103, 3203). In these cases the sulcus separating the two walls may have been very shallow and indistinct with a more or less cylindrical uterine cavity, such as have been seen in certain uteri removed at operation.

The only clinical significance that we have noted has been in those cases in which the two lobes lie, one anteriorly and one posteriorly, across the lateral uterine cavity sulcus, low in the uterus and near the cervix, to form placenta previa marginalis. We are of the opinion that such an extensive condition surrounding the cervix anteriorly and posteriorly has been mistaken for placenta previa centralis.

The following instances in which there was low implantation near the cervix are individually analyzed:

Fig. 3 (No. 649): Negro woman, aged 28 years, had a clinically diagnosed placenta previa with vaginal bleeding treated by rupture of the membranes. She delivered a normal infant, weighing 5 pounds 10 ounces.

Fig. 3 (No. 1217): White woman, aged 22 years, had low implantation without clinical evidence of placenta previa. She delivered a normal infant, weighing 8 pounds 2 ounces.

Fig. 4 (No. 1695 A): White woman, aged 32 years, had severe bleeding one month or more prior to spontaneous delivery at eight months, when she bled moderately, but blood was replaced by transfusion. She died on the second post-partum day, and autopsy revealed acute yellow atrophy of the liver. The edge of the placenta at the internal os of the cervix had a firm fibrotic necrotic retracted margin as is often found in placenta previa. The premature infant weighing 3 pounds 4 ounces was delivered by Willet forceps to the scalp. The infant died at one month of age.

Fig. 3 (No. 2199): White woman, aged 40 years, had no clinical evidence of placenta previa, and her infant was normal.

Fig. 3 (No. 2507): White woman had clinical evidence of low implantation and delivered a normal 9-pound infant.

Fig. 4 (No. 2578 A): White woman, aged 24 years, bled before delivery and had clinical diagnosis of placenta previa which was treated by rupture of the membranes. She delivered a normal premature infant, weighing 3 pounds 8½ ounces.

Fig. 3 (No. 2808): White woman, aged 22 years, had no clinical evidence of placenta previa. She delivered a normal infant, weighing 7 pounds 1 ounce.

Fig. 4 (No. 3905): White woman, aged 30 years, had no clinical evidence of low implantation. She delivered a normal infant, weighing 8 pounds 1 ounce. A study of the sac revealed low implantation complicated by hydramnios. The sac required 6,700 c.c. to distend it. The placenta weighed 692 Gm.

Fig. 4 (No. 3932 A): White woman, aged 42 years, had no clinical evidence of placenta previa. She delivered a normal premature infant, weighing 3 pounds 10 ounces.

#### SUMMARY

1. Previous studies of multiple-lobed placentas have been in the main confined to the report of a few cases found at the termination of labor, and from these the authors have developed the various theories as to formation.

2. From this present study of a large series by the fetal sac distention method, it has been found that most of the placentas consist of only two lobes, one of which is usually primary and much larger than the other.

3. It is also apparent that the two lobes usually lie one on the anterior and one on the posterior wall of the uterus and that the two lobes are joined together either at the side of the uterine cavity or over the apex of the uterine cavity.

4. The etiologic factor is considered to be fortuity, in that the fertilized ovum chanced to implant near one lateral or near the apical sulcus or fissure of the uterine cavity, and consequently trophoblastic invasion took place into both anterior and posterior endometrial walls, often more into one than into the other.

5. The condition has been shown to occur in abortion specimens but not relatively more often than in full-term sacs, and, therefore, it must not be a causative factor in premature onset of labor.

6. The condition has been shown to be associated not infrequently with low implantation of the placenta, forming a double type of placenta previa. This probably has been mistaken for placenta previa centralis.

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#### REFERENCES

- (1) *Walder, H.*: Gynec. et obst. 35: 361, 1937. (2) *Podleschka, K.*: Zentralbl. f. Gynäk. 60: 2007, 1936. (3) *Bumm, E.* (Berlin): Berl. Klin. Wchnschr. 55: 871, 1918. (4) *Lahm, W.*: Zentralbl. f. Gynäk. 46: 696, 1922. (5) *Itzkin, S.*: Monatschr. f. Geburtsh. u. Gynäk. 83: 35, 1929. (6) *Rocst, F.*: Nederl. tijdschr. v. verlosk. en gynaec. 37: 67, 1934. (7) *Levy, G.*: Bull. Soc. d'obst. et de gynéc. 17: 662, 1928. (8) *Torpin, R.*: AM. J. OBST. & GYNEC. 35: 683, 1938. (9) *Idem*: J. Obst. & Gynaec. Brit. Emp. 45: 993, 1939. (10) *Wislocki, G. B., and Streeter, G. L.*: Contrib. Embryol. 27: 1, 1938. (11) *Philipps, E.*: Zentralbl. f. Gynäk. 56: 2256, 1932. (12) *Wislocki, G. B.*: Am. J. Phys. Anthropol. 18: 81, 1933. (13) *Delcœur and Dresberg*: J. des Sc. med. de Lille 38: 46, 1920. (14) *Steele, H. G.*: West Virginia M. J. 33: 515, 1937. (15) *Wislocki, G. B.*: Contrib. Embryol. 22: 173, 1930. (16) *Idem*: Ibid. 21: 83, 1930. (17) *Rucker, M. P.*: J. Obst. & Gynaec. Brit. Emp. 37: 99, 1930. (18) *Rhenter, Z., and Pigcaud, H.*: Gynec. et obst. 18: 464, 1928. (19) *Wislocki, G. B.*: Am. J. Anat. 36: 467, 1926. (20) *Idem*: Contrib. Embryol. Carnegie Inst. 23: 165, 1932. (21) *Schiffmann, J.*: Zentralbl. f. Gynäk. 45: 754, 1921.

## ORAL PROGESTIN (ANHYDRO-HYDROXY-PROGESTERONE) IN THE TREATMENT OF DYSMENORRHEA\*

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THE experimental work of Knaus,<sup>1</sup> Novak and Reynolds<sup>2</sup> permits the conclusion that estrins augment and progestins inhibit uterine contractions. Kotz and Parker<sup>3</sup> found that 60 per cent of 50 patients with dysmenorrhea revealed a deficiency in corpus luteum as interpreted by the endometrial pattern from which bleeding occurred. These facts, it would seem, have provided a rational basis for the administration of progestin therapy in dysmenorrhea. On the other hand Wilson and Kurzrok<sup>4</sup> found that in the human being the maximal amplitude in uterine contractions occurred during the luteal phase and hence interdicted the use of progesterone therapy. Sturgis and Albright<sup>5</sup> relieved dysmenorrhea by inhibiting ovulation with estrins. However, further estrin therapy failed to prevent ovulation in the immediate successive period, and the dysmenorrhea recurred. This observation lends support to Wilson and Kurzrok's contention that "only women who have a corpus luteum can have functional dysmenorrhea." This maxim could not be substantiated by us.

In a series of some 75 patients with dysmenorrhea, endometrial biopsies were obtained immediately prior to, or at the onset of, menses in 53 instances. Three revealed a deficient progestinal endometrium of the mixed type. In 5 the bleeding was anovulatory, and of these 2 revealed a persistent estrogenic endometrium with a decidua-like stroma response. However, in 45 of the 53 biopsies, the endometrial pattern revealed excellent progestinal response, of which several had a pseudo-decidua reaction.

It would, therefore, seem illogical to administer progestin therapy to patients who have provided evidence of excellent utilization of their own corpus luteum, as reflected in their endometrial responses. In our experience this conclusion was borne out, for in general parenteral progesterone therapy proved disappointing except in those patients who showed evidence of corpus luteum deficiency. Two salient but contradictory facts are therefore apparent:

1. Painless menses occurring in anovulatory induced menstruation would seem to indict the corpus luteum!

2. Progesterone therapy proved useful in a series of patients who bled from an anovulatory or a deficient progestinal endometrium.

Urinary pregnanediol glucuronidate levels suddenly drop two or three days prior to onset of menses, as Venning and Browne,<sup>6</sup> Hamblen,<sup>7</sup> and

\*Read at the Fourth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Jacksonville, Florida, February 7 and 8, 1941.

Cope<sup>8</sup> and others have pointed out. This fact, which we have been able to corroborate, probably indicates complete cessation of corpus luteum activity and may account for the dysmenorrhea in spite of the progestinal type of endometrium from which bleeding occurred. The possibility that utilizable progestin during this deficient period could be made continuously and conveniently available through oral progestins prompted us to reopen this problem of the treatment of dysmenorrhea in spite of our previous disappointment with parenteral progestins. This communication deals with the treatment of dysmenorrhea by per oral administration of anhydro-hydroxy-progesterone. This product synthesized by Inhoffen, Longemann and Serini<sup>9</sup> is also known as pregnenolone. It is very potent orally and possesses progestinlike action among other biologic properties. This compound is closely related chemically to testosterone and progesterone, and has been shown to have progestomimetic activity when administered orally in immature rabbits,<sup>10</sup> and to produce in human beings a progestinal effect on the estrogen-primed endometrium.<sup>11, 12</sup> It has been used successfully to induce bleeding in cases of functional amenorrhea<sup>13</sup> and to control bleeding in menorrhagia.<sup>14</sup> It has also been demonstrated that this compound possesses estromimetic (immature rats) and andromimetic activity (capons and rats) in certain experimental animals.<sup>15</sup> These latter biologic properties could not be demonstrated when used experimentally in the human female.<sup>16</sup>

#### PROCEDURE

The present study is in the nature of a preliminary report, and was conducted on a series of 30 patients whose ages ranged from 19 to 39 years. Fifteen were married women, and of these only 2 had previously borne children, another became pregnant during treatment, and a fourth became pregnant immediately following cessation of therapy. Six had been sterile for two or more years. All patients were free of pelvic disease, except one who had a bilateral salpingectomy and still has a residual mass in one adnexal region. Five patients had retroverted uteri, and in 3 of these, it appeared that the uterus was infantile. In 2 others the uterus was somewhat bulkier or larger than normal. Endometrial biopsies were obtained in 17 of the 30 patients. In all but 4 instances the endometrial pattern was secretory. Of these, three had a persistent estrogenic endometrium, one had a cystic glandular hyperplasia. Biopsies were usually performed a few days prior to or on the day of onset of menses.

The 30 patients received oral progestin medication from 1 to 5 cycles, for a total of 64 cycles. Ten of these patients also received at some time or other parenteral progestin therapy. Sixteen additional patients who received progestin parenterally but not orally served as a basis for comparative study.

#### SIDE EFFECTS

Side reactions incident to the use of this drug were very few. Anhydro-hydroxy-progesterone was used not only in the present series of dysmenorrhea cases (30 patients), but also in other groups such as premenstrual tension, menorrhagia, etc., totaling some 45 cases. Only 2 patients complained of nausea and 1 complained of depression and slight dizziness. Cohen and Stein<sup>17</sup> claimed that 31 per cent of their patients complained of nausea, vomiting, abdominal pain, weakness, and dizziness or severe headache. Burge,<sup>18</sup> in the discussion of Cohen and Stein's paper, was at variance on this point and insisted that none of his 21 patients experienced undesirable reactions. Hamblen and his associates<sup>14</sup> witnessed no ill effects in their series. None of our patients developed any of the arrhenomimetic phenomena, skin rashes or acne. One volunteer dysmenorrhea-free patient was given 20 mg. for two days prior to onset of menses, and experienced a moderate degree of pelvic discom-

fort, with pains radiating down her thighs. Diminution of libido was noted in several patients in whom a tumescence of the sexual urge was manifested during the week prior to onset of menses.

### DOSAGE

The dosage varied from 20 to 240 mg. per month, and was administered orally in 5 to 15 mg. doses per day for varying periods of two to twenty-two days prior to onset of the succeeding menses. Occasionally medication was stopped several days prior to onset of the period, and on other occasions medication was carried along through the first few days of menstruation. The usual dosage was 5 or 10 mg., daily for the twelve days in the latter half of the cycle.

### RESULTS

The evaluation of pain is a variable and personal factor. When the patient experienced from 80 to 100 per cent relief for the period, it was interpreted as a satisfactory result. When the relief was less than 80 per cent but more than 40 per cent, it was regarded as a partial improvement. When the relief was less than 40 per cent, it was considered as a failure. Fifty per cent of the cycles were satisfactorily relieved, 22 per cent partially so, and 28 per cent were considered as failures. Several of the patients continued to experience satisfactory results from one to several months after cessation of therapy. Frequently, patients who experienced moderate or no relief after the initial trial of therapy obtained good results with continued therapy. Then again, the results for individual cycles in the same individual often varied. It must be mentioned that premenstrual tension, mastalgias, hypermenorrhea, and menstrual headaches associated with dysmenorrhea were often relieved.

### ENDOMETRIAL BIOPSY STUDIES

Oral progestin therapy did not interfere with ovulation when administered through the intermenstruum in 5 mg. doses per day. When biopsies were performed eight or ten hours after the onset of two consecutively treated but painless menses, a progestinal endometrium was obtained on both occasions. One patient with severe dysmenorrhea bled from an endometrium which was cystic glandular hyperplasia in type. She was treated with oral progestin for 2 cycles with excellent results. At the onset of menses of the third cycle for which no therapy was administered, a progestinal endometrium was obtained. When this procedure was repeated prior to the onset of the fifth menstrual period, a progestinal endometrium was again obtained. This patient now has remained free from dysmenorrhea for six months since cessation of therapy. This is particularly noteworthy, for hitherto in her twenty-three-year menstrual career, severe cramping pain was a constant feature of every menstrual period.

### ANALYSIS OF SUCCESSES AND FAILURES

At this stage, we are unable to surmise as to what physiologic action can account for the excellent results when obtained. Is it psychologic? In spite of the considerations which many investigators attach to psychogenic therapy, we feel that our control series ruled out this phase of the problem. Capsules of histaminase were administered to a group of 20 patients with dysmenorrhea for 1 to 3 cycles, and only two patients were benefited. Can the good results be due to increased progestin utilization? This question is difficult to answer. Urinary pregnanediol studies were performed on 11 patients with dysmenorrhea, and titers were obtained that were more or less similar to those of other groups. The administration of oral progestin was followed frequently by decreased urinary pregnanediol levels, whereas increased values often were obtained in the same patients when treated with estrins. Hamblen and associates,<sup>14</sup> have recently shown that oral progestin intake was not followed by alterations in urinary pregnanediol titers. Failures were most often encountered following the initial trial. One patient received from 70 to 180 mg. of oral progestin per month for three consecutive cycles without relief. Certain patients who obtained relief during some cycles experienced pain with other cycles. At times this was attributed to decrease in the dosages administered, at other times this was noted

following increase in dosages. Whether failures or successes depend on the relationship of oral progestin intake to meals, as yet has not been ascertained. It may well be that this steroid, anhydro-hydroxy-progesterone, should be taken with a fat meal or with bile salts to promote better absorption or utilization. The modus operandi of oral progestin in the therapy of dysmenorrhea is not as yet clear. Lackner and his associates,<sup>19</sup> Elden and Wilson,<sup>20</sup> obtained satisfactory results in certain groups with parenteral progestin therapy. This much is certain, that many patients who failed to respond to parenteral progestin therapy in our own series obtained partial to complete relief following oral progestin administration.

### CONCLUSIONS

1. Oral progestin (anhydro-hydroxy-progesterone) was administered during 64 cycles in 30 patients with dysmenorrhea. Fifty per cent of the cycles were satisfactorily relieved, 22 per cent partially so, and 28 per cent were considered as failures.

2. Endometrial biopsies were performed in 17 of the 30 patients just prior to, or immediately after, the onset of menses. Excellent progestinal responses were obtained in 13 instances, and in 4 the bleeding was anovulatory.

3. Oral progestin therapy frequently was followed by relief in patients who failed to respond to parenteral progestins. Premenstrual tension, mastalgias, menstrual headaches, when associated with dysmenorrhea, often were relieved by oral progestin therapy. Concurrent abnormalities in the menstrual flow were often stabilized.

4. Response to therapy did not depend on size and position of uterus nor on dosage employed. Results were variable in the same individual. Increase or decrease in dosage was liable to be followed by pain.

5. Undesirable side reactions such as nausea, dizziness, etc., were very infrequent. The authors believe the substance innocuous if used in dosages up to 240 mg. per month. Oral progestin therapy did not interfere with ovulation. One patient became pregnant during therapy, and another immediately after cessation of therapy.

The oral progestin (anhydro-hydroxy-progesterone), used in this investigation, was kindly furnished as Pranone by W. H. Stoner, Schering Corporation. Other synonyms for this product are pregnenolone and 17-ethinyl testosterone.

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### REFERENCES

- (1) Knaus, H.: Arch. f. Gynäk. 138: 201, 1929. (2) Novak, E., and Reynolds, S. R. M.: J. A. M. A. 99: 1466, 1932. (3) Koltz, J., and Parker, E.: AM. J. OBST. & GYNEC. 37: 116, 1939. (4) Wilson, L., and Kurczok, R.: Endocrinology 27: 23, 1940. (5) Sturgis, S. H., and Albright, F.: Ibid. 26: 68, 1940. (6) Penning, E. H., and Browne, J. S. L.: Ibid. 21: 722, 1937. (7) Hamblen, E. C., Powell, N. B., and Cuyler, W. K.: AM. J. OBST. & GYNEC. 38: 557, 1939. (8) Cope, C. L.: Clin. Sc. 4: 217, 1940. (9) Inhoffen, H. H., Longemann, W., and Serini, A.: Ber. Deutsch. Chem. Ges. 71: 1024, 1938. (10) Inhoffen, H. H., and Hohlweg, W.: Naturwissenschaften 26: 96, 1938. (11) Clauberg, C., and Ustun, Z.: Zentralbl. f. Gynäk. 62: 1745, 1938. (12) Salmon, U. J., Walter, R. I., and Geist, S. H.: Proc. Soc. Exper. Biol. & Med. 40: 252, 1939. (13) Zondek, B., and Rozin, S.: Lancet 1: 504, 1939. (14) Hamblen, E. C., Powell, N. B., Cuyler, W. K., and Pattee, C. J.: Endocrinology 26: 201, 1940. (15) Emmens, C. W., and Parkes, A. S.: Nature 143: 1064, 1939. (16) Salmon, U. J., and Geist, S. H.: Proc. Soc. Exper. Biol. & Med. 45: 522, 1940. (17) Cohen, M. R., and Stein, I. F.: AM. J. OBST. & GYNEC. 40: 713, 1940. (18) Burge, E. S.: In discussion of paper by Cohen and Stein. (19) Lackner, J. E., Krohn, L., and Soskin, S.: AM. J. OBST. & GYNEC. 34: 248, 1937. (20) Elden, C. A., and Wilson, K. M.: Ibid. 32: 91, 1936.

## STERILIZATION IN THE PUERPERIUM\*

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AN IMPORTANT factor in the reduction of maternal deaths is the prevention of pregnancy in those individuals whose physical condition makes repeated childbearing unusually hazardous. About 95 per cent of the women in the higher social and intellectual groups can successfully prevent pregnancies by the use of the various mechanical contraceptive devices. Many clinic patients, however, cannot successfully use contraceptive measures, and for these, some type of operative sterilization must be employed if rapidly repeated pregnancies are to be avoided. Contraceptive advice is given, when indicated, as a part of the routine care in our post-partum clinic. Unfortunately, only a small percentage of our public ward patients have been successful in the use of contraceptive measures, in spite of the fact that only those whom we presumed to have sufficient ability and intelligence to use the methods, were so advised.

It was generally the custom to perform sterilizing operations some months after delivery, usually as a part of a gynecologic repair operation. This required a second hospital admission with its additional expense and period of disability, and not infrequently another pregnancy would occur before the patient returned for the repair and sterilization. Some obstetricians have at times effected delivery by cesarean section, primarily for the purpose of sterilization, although we have never felt that sterilization alone was sufficient justification for abdominal delivery.

In 1932, Skajaa<sup>1</sup> pointed out the feasibility of performing sterilizing operations during the puerperium and reported 126 cases done between the second and twenty-ninth post-partum days. In 1939, Adair and Brown<sup>2</sup> reported 50 cases of puerperal sterilizations done within twenty-four hours after delivery. In 1940, Russell<sup>3</sup> recorded 29 cases done at intervals varying from one hour to thirteen days after delivery, and in the same year Hewitt and Whitley<sup>4</sup> recorded 100 cases performed one hour after delivery.

During the five-year period from July 1, 1935, to June 30, 1940, 309 sterilizations were performed during the puerperium on the Obstetrical and Gynecological Service at the University of Virginia Hospital. In the present report, we wish to present an analysis and review of these cases.

### PERMISSION

Aside from the Virginia law for compulsory sterilization of mental defectives and those with presumably inheritable mental disease, there is no law in Virginia regarding contraception or sterilization. It is our custom to require a written request and permission for sterilization, to be signed by both the woman and her husband in the presence of witnesses.

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The average age of this group of 309 patients was 29.4 years, the youngest 18 and the oldest 45 years. Two hundred and forty-four were white and 65 were colored patients.

### INDICATIONS

The indications for sterilization in this group are shown in Table I.

TABLE I. INDICATIONS FOR STERILIZATION

INDICATION	NO.
Excessive multiparity	175
Hypertension and/or nephritis	84
Cardiac and vascular diseases	15
Nervous and mental diseases	10
Secondary perineorrhaphy (at delivery)	9
Pyelitis and pyonephrosis	7
Miscellaneous causes (1 case each)	9
Total	309

The largest group is made up of those in whom we have given the indication as excessive multiparity. This group consists mainly of those from the lower social, economic, and intellectual group, in whom the use of even the simplest types of contraceptive materials is too complicated and expensive for them, as is proved by our experience in the post-partum clinic. Many of them are from the mountainous areas in our vicinity and most of them are completely indigent, applying repeatedly for admission to the hospital on free beds. The 175 women in this group had had a total of 1,161 pregnancies or an average of 6.63 pregnancies per woman, with extremes from a minimum of 3 to a maximum of 15 pregnancies. Hypertension and renal disease was the indication in 84 instances, all in multiparous individuals, one of whom had had 15 pregnancies. In 9 instances, a secondary perineorrhaphy was done at the time of delivery because of old lacerations and relaxations of the perineum, and was followed by sterilization in the immediate puerperium.

### METHOD

There has been some discussion as to the proper time in the puerperium to perform a sterilizing operation. It is our belief that, as far as morbidity is concerned, a proper selection of cases is more important than the time at which the operation is done. We feel that the procedure should be avoided in those whose labors have been such that potential infection may be assumed to be present. We have done sterilizations at time intervals varying from a few hours post partum to the twenty-first post-partum day. The main advantage of early post-partum sterilization is the decrease in the length of hospitalization. At present we perform the operation as early in the puerperium as is feasible, dependent on the type of labor, the condition of the patient, and the presentation of the necessary permits. We do the operation at a scheduled time on regular operating days, which is, of course, impossible if the operations are routinely done one hour post partum.

The anesthesia employed seems to be purely one of personal preference and experience of the anesthetist and surgeon. We prefer spinal anesthesia, which is the anesthesia most commonly used in our hospital for abdominal surgery. Two hundred and ninety-seven of the cases were done with spinal anesthesia, using 150 mg. of procaine. Nine were done under general anesthesia and 3 under local infiltration.

Unhappily none of the methods of operative sterilization short of complete castration seem to be 100 per cent effective. The multiplicity of operative procedures, which consist mainly of various gymnastic procedures on the Fallopian tubes, attest to their lack of perfection in results. Of the 309 sterilizations in the present report, 219 of them have been done by the Pomeroy technique. Formerly with this method we used No. 1 or No. 2 chromic catgut for the ligature, but during the past year we have been using No. 1 plain catgut exclusively. Eighty-six of the early cases were done by a method which we speak of as segmental resection. This seems to be a modification, proposed by Fritsch,<sup>5</sup> of the Kehrer method. With this technique



a segment of the tube was excised and the proximal extremity doubly ligated with heavy black silk and the distal end singly ligated with silk. The Madlener technique was used three times and cornual excision once.

The procedure is carried out through a subumbilical incision of approximately one and one-half inches in length. Manipulation of the pelvic structures is avoided, the tube being simply exposed with a sponge stick or Babcock clamp, lifted in its midportion, identified by its fimbriated extremity, and the sterilizing procedure carried out. If the appendix is easily available it is removed. For the past year, we have been closing the abdominal incision with fine black silk.

#### MORBIDITY

In the 309 cases of sterilization, 66, or 21 per cent, had morbidity on the basis of the standard of morbidity adopted by the American Committee on Maternal Welfare (100.4° F. or over on any two days after the first twenty-four hours post partum, oral temperatures taken at least four times daily). Of these 66, only 12 had sufficient elevation or prolongation of fever to interfere with discharge from the hospital at the usual time. The average duration of the fever for all of the cases of morbidity was two days. Our incidence of morbidity is higher than those quoted by Adair and Brown,<sup>2</sup> 12 per cent, but their patients were operated upon in twenty-four hours which would eliminate elevations on the day of operation as a part of the morbidity. Our morbidity includes those elevations on the day of operation, except those that were done in the first twenty-four hours.

The complications are shown in Table II.

TABLE II. COMPLICATIONS

DIAGNOSES	NO.	DAY P. P. OPERATED	REMARKS
Endometritis	3	2, 3, and 5 days	1 version and extraction
Pyelitis	3	2, 4, and 12 days	
Pneumonia	2	9 and 11 days	1 acute appendicitis
Multiple pulmonary emboli	1	3 days	Retrocecal appendix Obesity, 218 pounds
Thrombophlebitis	1	2 days	Perineorrhaphy
Atelectasis	1	2 days	
Diabetic acidosis, pyelitis, pneumonia	1	9 days	Died
Total	12		

One death occurred in this series of 309 patients. This was a thirty-four-year old colored multipara with a severe diabetes and hypertension, for which labor was induced by rupture of the membranes, followed by delivery of an excessive-sized child. The diabetes was still poorly controlled post partum; however, she was sterilized on the ninth post-partum day. She developed pyelitis and pneumonia and went into a severe acidosis and died on the sixth postoperative day. It was an error to have sterilized her, as the diabetes was poorly controlled, and her general condition was unsatisfactory.

The one patient with thrombophlebitis had a secondary perineorrhaphy at the time of delivery and was sterilized thirty-six hours later. Phlebitis appeared on the eighth post-partum day and required a total hospital stay of thirty days. The patient with multiple pulmonary emboli was sterilized on the third post-partum day and had a total period of hospitalization of thirty-one days. Both patients with pneumonia recovered and were discharged from the hospital on the sixteenth postoperative day.

The appendix was removed at the time of sterilization in 178 of the 309 patients. In 140 of these there was no morbidity, and in the 66 instances of morbidity, the appendix had been removed in only 38. The appendix was not removed in the one fatal case. The removal of the appendix apparently had no appreciable effect on the convalescence or on the incidence of morbidity.

When the febrile cases are analyzed in relation to the time post partum that the operation was done, no constant relationship is found. This is interesting because

Skajaa,<sup>1</sup> Adair and Brown,<sup>2</sup> and Russell<sup>3</sup> have emphasized the dangers of sterilization after the first post-partum day. Skajaa<sup>1</sup> in his report had 46 patients who were operated upon between the fifth and twenty-ninth post-partum days, and in these there were 8 cases of thrombosis and embolism; 5 of them occurring in 12 cases done on the fifth and sixth days. The 2 patients with thrombosis and embolism which occurred in our 309 patients, were operated upon on the second and third days, respectively. The number operated upon on the different post-partum days with the number and percentage of cases with fever and complications for those days are shown in Table III. The time post partum that the operation is performed does not seem to be associated with any significant variations in the incidence of morbidity or complications.

TABLE III. DAY OF OPERATION WITH MORBIDITY

P.P. DAY	NUMBER OF OPERATIONS	NUMBER WITH MORBIDITY	COMPLICATIONS	PER CENT MORBIDITY
1	12	1	0	8
2	47	9	{ Endometritis 1 Pyelitis 1 Atelectasis 1 Thrombophlebitis 1	19
3	64	9	{ Endometritis 1 Pulmonary Emboli 1	14
4	47	12	Pyelitis 1	25
5	27	6	Endometritis 1	22
6	10	0		0
7	17	1		6
8	27	12		44
9	17	5	Pneumonia 2	30
10-21	41	11	{ Pyelitis 1 Pneumonia 1	26
Totals	309	66	12	21

TABLE IV. STERILIZATIONS BY YEARS WITH MORBIDITY

YEAR	NUMBER	AVE. P.P. DAY DONE	AVE. DAYS IN HOSP. P.O.	AVE. TOTAL HOSP. DAYS	NUMBER WITH MORBIDITY	COMPLICATIONS	PER CENT MORBIDITY
1935	5	12.4	13	25	3	0	60
1936	20	9.5	9.8	19.3	7	1	35
1937	55	9.5	6.9	16.4	12	2	22
1938	75	4.8	6	10.8	17	2	23
1939	91	3.3	6.3	9.6	24	7	26
1940	63	3.2	5.1	8.3	3	0	5
Total	309				66	12	
Averages		5.2	6.4	11.7			21

In Table IV the cases are presented by years, showing the average post-partum day upon which the operation was performed during that year, the average length of postoperative stay in the hospital, as well as the number of febrile cases and complications for each year. Each year we have gradually shortened the interval between delivery and sterilization as well as the postoperative period of hospitalization. With the exception of the years 1935 and 1940, there is no appreciable difference in the incidence of morbidity. The morbidity incidence of 60 per cent in 1935 seems without significance because there were only 5 cases for the half of that year under consideration. In 1940 the interval between delivery and sterilization was essentially the same as for 1939, so there seems to be no obvious explanation in the time interval for the lower incidence of morbidity in 1940. Of the 63 cases done in 1940, the abdominal incision was closed with catgut in 25 and

with black silk in 38. The 3 cases of morbidity (12 per cent) which did occur, were in those 25 cases in which the incision was closed with catgut. There were no instances of fever in the 38 patients in whom the incision was closed with black silk. In 1940 the patients averaged a total hospital stay of 8.3 days for both delivery and sterilization, with an average interval of 3.2 days between delivery and sterilization.

### FOLLOW-UP

Ordinarily it is assumed that subsequent information is unnecessary in order to determine the effectiveness of sterilization, inasmuch as the patient will undoubtedly seek out, often with some vindictiveness, the surgeon who operated upon her, in the event that a pregnancy should subsequently occur. However, we attempted to follow-up these 309 patients, and we have recently seen 107 and have had a letter from 119 of them stating that no pregnancies have occurred since the operation, a follow-up incidence of 73 per cent. An analysis of the follow-up information is shown in Table V.

TABLE V. FOLLOW-UP DATA

METHOD	NUMBER DONE	NUMBER FOLLOW-UP	FOLLOW-UP PERCENTAGE
Pomeroy	219	145	66
Segmental resection	86	77	90
Madlener	3	3	100
Cornual excision	1	1	100
Totals	309	226	Average 73

We have definite knowledge that 145, or 66 per cent, of the patients sterilized by the Pomeroy method, and 77, or 90 per cent, of the 86 sterilized by segmental resection have as yet had no pregnancies since sterilization. The 3 patients sterilized by the Madlener method and the one by cornual excision have been seen and are known not to have conceived. The patients seem quite appreciative in the answers to the follow-up letters, and except for occasional instances of menstrual irregularities, they have had no unusual symptoms. Unfortunately our letter seems to have disturbed the confidence of a few of them in the effectiveness of the operation, and will no doubt cause them some slight degree of mental anxiety for a few months.

### SUMMARY

We have presented a report of 309 cases of sterilization at varying intervals from the first to the twenty-first post-partum day.

Spinal anesthesia was used in 297, general anesthesia in 9, and local anesthesia in 3 cases.

The sterilization was done by the Pomeroy technique in 219, segmental resection with heavy silk ligatures in 86, by the Madlener method in 3, and cornual excision in 1 case.

The appendix was removed at the time of sterilization in 178 of the patients, without any appreciable effect on the convalescence or on the incidence of morbidity.

Sixty-six, or 21 per cent, had morbidity on the basis of the standard of morbidity determined by the American Committee on Maternal Welfare. Only 12 of these had postoperative complications requiring prolongation of the hospital stay.

There was one death, a patient with hypertension and diabetes who developed pyelitis and pneumonia and died on the fifth postoperative day in acidosis.

The time post partum at which the operation was performed seemed to show no definite statistical relationship to the incidence of morbidity or postoperative complications.

A yearly analysis of the cases is presented which shows a progressive decrease in the post-partum interval before operation and in the total period of hospitalization with each year. During the year 1940, sterilizations were done mostly on the third day, and the patients were discharged from the hospital on the average on the eighth post-partum day. During 1940 the incidence of morbidity was only 5 per cent and in 38 consecutive cases during that year in which the abdominal incision was closed with black silk, there were no instances of morbidity or complications.

Two hundred and twenty-six, or 73 per cent, of these 309 patients have been followed up either by examination or letter, and no subsequent pregnancies have occurred in them.

#### REFERENCES

- (1) Skajaa, K.: Acta. obst. et gynec. Scandinav. 12: 114, 1932. (2) Adair, F. L., and Brown, Ira: Am. J. Obst. and Gynec. 37: 472, 1939. (3) Russell, P. B.: South. M. J. 33: 424, 1940. (4) Hewitt, H. P., and Whitley, J. R.: AM. J. OBST. AND GYNEC. 39: 649, 1940. (5) Crossen and Crossen: Operative Gynecology, ed. 5, St. Louis, 1938, The C. V. Mosby Company.

## AN ELECTROMETRIC STUDY OF UTERINE ACTIVITY\*

### PRELIMINARY REPORT

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INVESTIGATORS have long recognized the necessity for a better understanding of the essential characteristics of human uterine behavior. Few of the methods of study have been entirely satisfactory. While much has been learned from experimental analysis, valid interpretations in terms of human physiology have been difficult. It is not surprising, therefore, that the success of the electrocardiograph and the electroencephalograph has stimulated the search for an electrical means of recording uterine activity. Two types of such procedure are available. One is to apply the techniques of recording alternating current changes in the manner similar to that of the electrocardiograph, and the other is to employ the more recently developed technique of recording changes in the direct current or standing potentials in the intact organism. The validity of either of these procedures must rest on one-to-one correlations between the changes in electrical activity and other known evidences of physiologic change.

#### PREVIOUS INVESTIGATIONS

Among the first attempts to record uterine activity are those which made use of manometric recording of volume changes in the uterus through flexible balloons

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(Dickinson).<sup>1</sup> Knaus<sup>2</sup> made observations on the human uterus in vivo by inserting an elastic bag into the uterus and recording uterine contractions on a kymograph. He found (a) spontaneous rhythmical contractions in regularly menstruating women during the first fourteen days, the uterus during this phase reacting to pituitary extract. (b) On the sixteenth day and lasting until menstruation begins, no spontaneous contractions occur, and the uterus does not contract with pituitrin injections. This follows according to Knaus, because of an inhibiting influence of the corpus luteum on the uterus. (c) When this failure to react to pituitrin does appear, Knaus assumes that ovulation has taken place within a definite time and used this as a means of determining the time of ovulation in the menstrual cycle. Kurzrok and others,<sup>3</sup> in a study of uterine motility, made by inserting a rubber balloon into the uterine cavity, filling the balloon with air and attaching it to a recording kymograph, failed to confirm the observation of Knaus. It should be noted that in these studies, Kurzrok stated that "dysmenorrhea occurs at the time when the uterine contractions achieve their greatest amplitude, i.e., just preceding and during the first few days of the menstrual flow."

Moir,<sup>4</sup> in a clinical comparison of ergotoxine and ergotamine, used a hydrostatic intrauterine bag to observe post-partum uterine contractions. Adair and Davis<sup>5</sup> observed the effects of oxytocic drugs on the human post-partum uterus by inserting rubber bags filled with water.

Paralleling these observations by mechanical methods are a number of studies involving electrical techniques. Observations on the human uterus have been made by Theilhaber,<sup>6</sup> Bode,<sup>7</sup> Veit,<sup>8</sup> and Falk and Nahon,<sup>9</sup> making use of the string galvanometer and associated equipment.

More recently Jacobson and others<sup>10</sup> reported observations on electrical and mechanical activity of the human nonpregnant uterus. Inserting two electrodes into the lips of the cervix, they concluded that contraction voltages of the uterus can be studied with the string galvanometer plus amplifiers, and showed that mechanical tracings parallel those made by electrical methods. Their method is elaborate and complicated. Vozza,<sup>11</sup> working with rabbit uteri, also concluded that there was a relationship between mechanical contractions and bioelectric phenomena.

#### PRESENT METHOD

In the studies which have so far been reported, difficulties have been encountered in the rather complicated techniques or in interpretation of the findings. It seemed worthwhile, therefore, to examine the possibility of applying the Burr-Lane-Nims<sup>12</sup> technique for recording standing potentials to this problem. The experimental findings resulting from the application of this technique to the study of estrous phenomena in experimental animals and more particularly the exact timing of ovulation in animals and in women suggested the possibility that the technique might be useful in studying uterine physiology.

In essence the method consists of connecting a vacuum tube microvoltmeter to the cervix of the uterus and recording the changes in voltage by means of a General Electric photoelectric recorder. The instruments, if so used, are capable of recording only relatively slow changes in the standing potential of the uterus. For the majority of the readings, the recording paper was traveling at the rate of six inches per hour, although at times this could be increased to six inches per minute. Ideally, the microvoltmeter should be connected to the cervix by reversible nonpolarizing electrodes, since it is well known that metal in contact with living tissues gives rise to an unstable and artificial contact potential. With such electrodes, accurate recording of the absolute potential difference can be made with certainty. How-

ever, the technical difficulties of applying such electrodes to the cervix made it seem advisable to sacrifice the absolute value of the potential difference in favor of a procedure which would record the changes in the standing potential, even though the latter were complicated by the presence of an artificial potential.

For this reason, the microvoltmeter was connected to the patient by means of wires terminating in metal clips which gripped the lips of the cervix. In practice, the cervix was exposed through a Sims' metal vaginal speculum. The clip electrodes and the wires connecting them to the instrument were insulated by rubber covering except for the terminal jaws. The ground electrode from the microvoltmeter was inserted into the posterior lip of the cervix and the hot electrode into the anterior lip. When repeated daily observations were made on the same patient, different sites were used for attachment of the electrodes, but the same polar relationships were maintained. The electrodes were applied with the patient in the dorsal lithotomy position after which the patient was made comfortable on the operating table with legs extended. The vaginal speculum remained in place throughout the period of recording and apparently caused no distress. Activity was necessarily limited during observations, but other than backache patients had no complaints except when uterine cramps were produced by injections of pituitrin and ergotrate. A sharp pain was produced momentarily in some patients at the time of attachment of electrodes to the cervix, but this disappeared almost immediately. In general, observations were made during periods of thirty minutes to three hours, the average time being two hours. In the daily observations on one patient (R. F.) covering a complete menstrual cycle, records were kept for a minimum of two hours. The corpus luteum was in all probability functioning in this patient, for she was the mother of four children. As might be expected, the metal-to-tissue electrodes gave a somewhat unstable base line with a considerable tendency to drift. This could be obviated to some degree by including larger amounts of tissue in the bite of the clips.

In the patients who were given pituitrin or ergotrate, and in one patient, receiving estradiol, recordings were run for a period of thirty minutes to one hour, preceding the giving of the preparation, so that ample time was allowed to observe the character of the spontaneous behavior of the uterus. Pituitrin and the sex hormone preparations were administered intramuscularly; ergotrate injected intravenously.

In the cyclic study made on one patient (R. F.), injections of progesterone were given at the completion of an observation, and recordings repeated subsequent days to determine the effect on the uterus.

The menstrual cycle (in all patients having menses) was dated from the first day of the flow, this being the usual method of calculation. While some investigators<sup>13, 14</sup> are of the opinion that a new cycle begins three to five days after the onset of a period, it was deemed preferable to consider the first day of bleeding as No. 1 in the cycle. The study of one menstrual cycle is complete, so that conclusions can easily be interpreted by either method of calculation. No endometrial studies were made.

## RESULTS

a. *Normal Case.*—In the present study, 56 sets of observations were made on 17 patients distributed as indicated in Table I. Case 1 was a 27-year-old woman, the mother of four children. The electrometric recording on successive days of one complete menstrual cycle is shown in Fig. 1. As a check on these, seven additional days from other cycles are included in the figure to demonstrate that

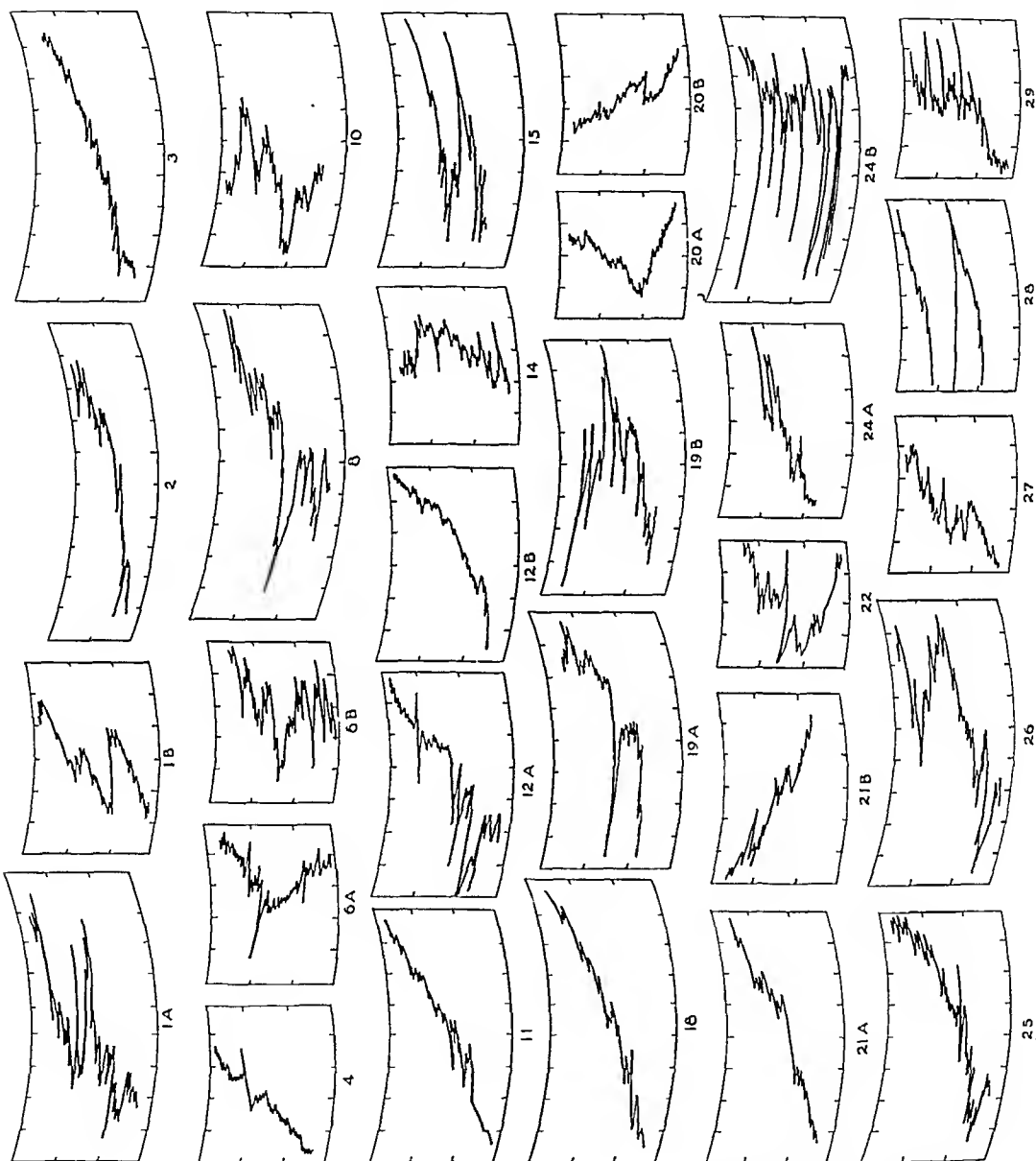


Fig. 1.—Electrometric records of successive days of the menstrual cycle of Case 1. Numbers refer to days of cycle. Duplicate days of other cycles bear letters. Note especially activity at beginning and end of cycle.

the character of the curve is similar on corresponding days. It should be noted that during the first day of the cycle, there was considerable activity. During the second, third, and fourth days uterine activity was less marked. From the sixth to the tenth day, activity increased to be followed on the eleventh day by a quiet period. The twelfth to the fifteenth days were again active with a quiet

eighteenth day. The nineteenth day was active but the twentieth to the twenty-fourth days showed only a moderate degree of activity. Beginning the twenty-fourth and continuing to the twenty-seventh, activity was more marked and, with the possible exception of the twenty-eighth, this continued until the end of the twenty-ninth day. These studies indicate that uterine activity is not a constant finding throughout the cycle nor is it confined to any part of the cycle but comes and goes. Information regarding the physiology of the uterus during the entire cycle is too fragmentary to indicate any possible correlations with electrical activity.

TABLE I. A TOTAL OF 56 RECORDINGS WERE MADE ON 17 PATIENTS

Total number of patients, 17; and total number of observations, 56

PATIENTS	AGE	TYPE OF CASES OR STATUS OF PATIENT
1. R.F.	27	Daily observations of a complete menstrual cycle
2. N.H.	26	Dysmenorrhea beginning 7 days premenstrual. Tenth day of cycle. Suspension of uterus 6 mo. prior to recording
3.	30	Seventeenth day of cycle
4. M.S.	32	Eighth day of cycle. Left ectopic 2½ yr. ago
5.	53	2 yr. postmenopause
6.	65	23 yr. postmenopause. Patient receiving ovarian hormone, record similar to Case 6
7.	17	Seventeenth, eighteenth and nineteenth day postmenses
8.	19	3 days post dilatation and curettage
9. D.G.	17	6 days postmenses. Observations before and after 1 c.c. of ergotrate, given intravenously
10.	21	18 days postmenses, observations before and after ergotrate
11.	17	22 days postmenses, observations before and after pituitrin
12.	28	8 days postmenses, observations before and after pituitrin
13.	24	11 days postmenses, observations before and after pituitrin
14. S.H.	46	Menopause syndrome, menses irregular and scanty, given 10,000 R.U. of estradiol benzoate and observations made 24 hours later
15. C.M.	45	Menorrhagia of menopause, 2 days post dilatation and curettage
16. H.G.	49	Spontaneous menopause 1 yr. Has had 2 menstrual periods in past yr. Received 20,000 I.U. ovarian hormone in past two weeks
17.	27	Fifteenth day postmenses, normal periods

There were no similar potential changes recorded with the application of both electrodes to the anterior lips of the cervix or on attaching one electrode to the cervix and one to the vaginal mucous membrane.

*b. Menopause Cases.*—As a control for this group of determinations, recordings were taken from a number of cases of menopause. Some of these graphs are charted in Fig. 2. A brief sample from a forty-six-year-old menopausal patient is shown in Fig. 2, *A*. This obviously is a quiet uterus. In Fig. 2, *B* is the record of a 53-year-old patient with flushes and headaches two years after the onset of menopause. This record seems to be quite characteristic of active uterine contractions. In Fig. 2, *C* is recorded a case of menorrhagia of menopause two days after a dilatation and curettage. This is obviously a relatively inactive uterus. In Fig. 2, *D* is shown the records of a patient with spontaneous menopause of one year's duration who had received over twenty thousand international units of ovarian hormone in the last two weeks. This record points to the possibility that the administration of ovarian hormone has increased uterine activity.

*c. Effect of Drugs.*—The effect of other drugs on the uterus is shown in Fig. 3. In Fig. 3, *A* is a record taken from a 17-year-old patient six days postmenses. This is obviously a moderately active uterus. At the beginning of the record in Fig. 3, *A'*, 1 c.c. of ergotrate was given intravenously. The following fifteen minutes of record show a very marked increase in the electrical activity. In Fig. 3, *B* a similar record from a 21-year-old patient, eighteen days postmenses is shown. One cubic centimeter of ergotrate was introduced intravenously at the point marked with the arrow and thirty minutes later as shown in Fig. 3, *B'*, electrical



activity has increased considerably and cramps reported as indicated by the arrow. In Fig. 3, *C* is a record from a 24-year-old patient, eleven days postmenses. The records show a moderately quiet uterus. Fifteen minutes after the injection of  $\frac{1}{2}$  c.c. of pituitrin, the record shown in Fig. 3, *C'* gives evidence of a considerable increase in uterine activity.

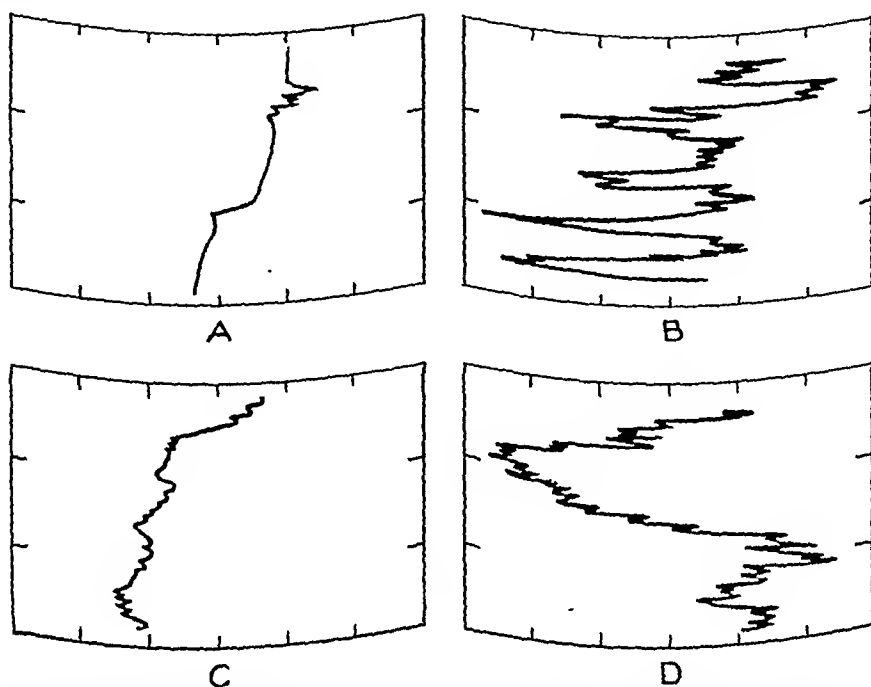


Fig. 2.—Records of menopause. *A*, 46-year-old patient; *B*, 53-year-old patient, with flushes and headaches; *C*, menorrhagia; and *D*, 49-year-old patient, with estrone.

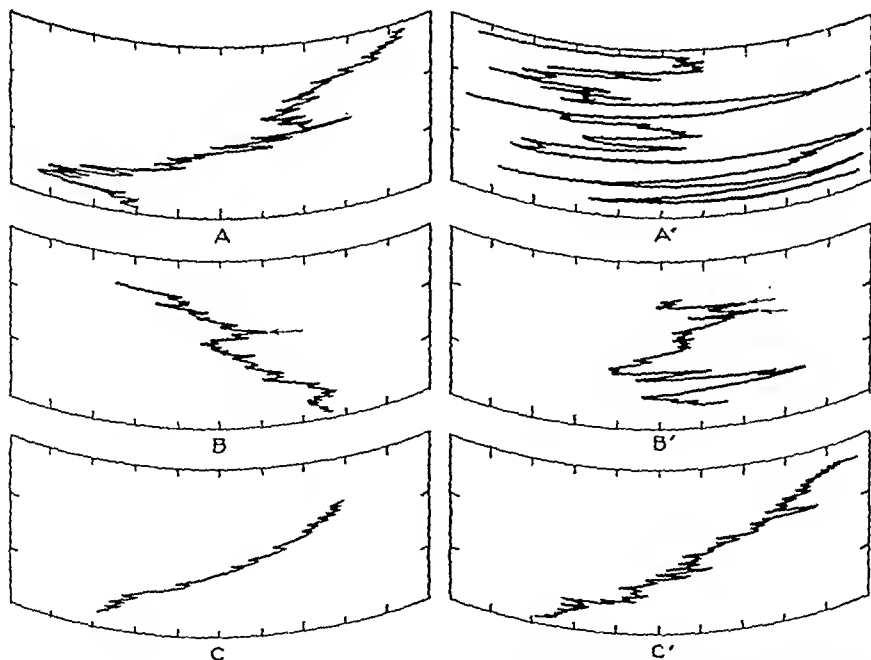


Fig. 3.—Records of young patients. *A*, 17-year-old patient, before ergotrate; *A'*, 17-year-old patient, after ergotrate. *B*, 21-year-old patient, before ergotrate; *B'*, 21-year-old patient, after ergotrate. *C*, 24-year-old patient, before pituitrin; *C'*, 24-year-old patient, after pituitrin.

The effect of 10,000 rat units of estradiol benzoate is shown in Fig. 4 with records taken from a 46-year-old patient, showing the menopause syndrome with irregular and scanty menses. In Fig. 4, *A* is a record taken at the time of administration of the hormone as indicated by the arrow. In the succeeding hour, no essential change in the record occurred, the electrometric records being characterized by relatively little uterine activity. Twenty-four hours later the record showed a marked change. In Fig. 4, *B* the first five minutes of the record taken at slow speed shows a very great increase in electrical activity. In the upper part of the figure this activity was resolved by increasing the speed of the paper to six inches per minute. It will be noted in the portion marked "fast" that the electrical record shows wide swings at relatively high frequency. During this period, the patient complained of cramps.

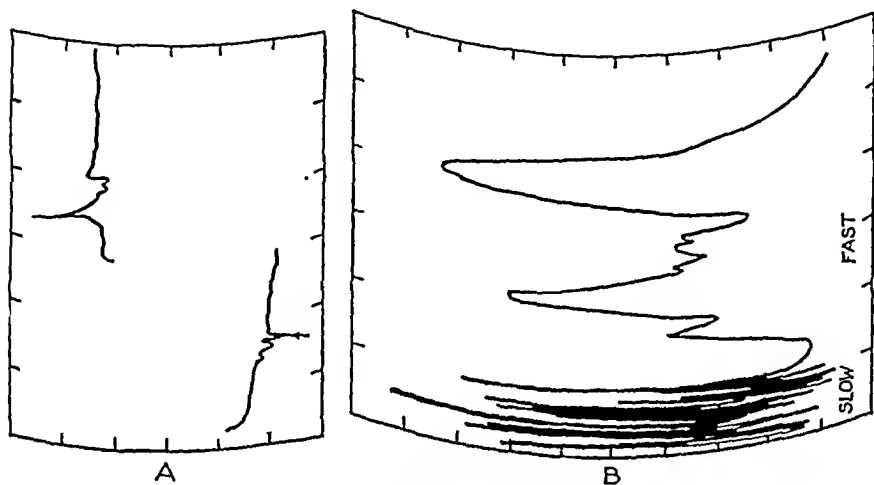


Fig. 4.—Records of menopause. *A*, Before estradiol benzoate at arrow; *B*, after estradiol benzoate.

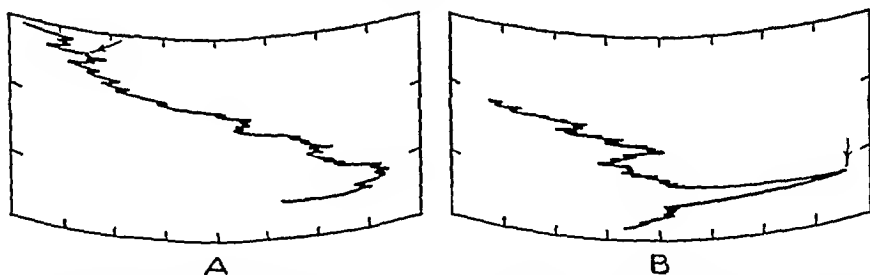


Fig. 5.—Records of 28-year-old patient. *A*, Before administration of pituitrin, at arrow; *B*, twenty-five minutes after, showing wide swing with report of cramp, at arrow.

The correlation of sharp increases in potential difference with cramps had been noted in Case 1, in which dysmenorrhea was present. A reference to Fig. 1 will also show that on the first day of the cycle, and during the last five days of the cycle, there were wide voltage swings. At the time of their occurrence the patient reported a cramp. In fact, it was possible to predict the onset of a cramp by watching the electrical record before the patient reported it. As a further check on this, three patients were studied at varying times in the cycle following the administration of pituitrin. In Fig. 5 a record is shown from a 28-year-old patient eight days after menses. This record shows in Fig. 5, *A* that the uterus is fairly quiet until the administration of 0.5 e.c. of pituitrin, as indicated by the arrow. In Fig. 5, *B*, twenty-five minutes later, is shown a fragment of a record which included a wide swing and a report of cramps at the point marked with the arrow. Finally, it must be recorded that in Case 1, a patient suffering from

dysmenorrhea, the administration of progesterone beginning on or about the twentieth day of the cycle, markedly reduced, if it did not entirely obliterate, cramps. A further study with more exact techniques will be required to elucidate more certainly the relationships between electrical activity of the uterus and cramps.

#### DISCUSSION

Evidence that the intact human uterus produces direct current characteristics is presented. The potential differences are not chaotic, but produce patterns which are characteristic of uterine motility. Furthermore, the normal spontaneous activity of the uterus, interpreted as contractility, can be recorded with sufficiently constant characteristics to make it possible to state that spontaneous contractions occur in the uterus throughout the entire menstrual cycle, but that deviations from this characteristic pattern can be recognized.

The marked exaggeration of contractions in a patient with spontaneous cramps is comparable to the effect following injections of pituitrin or ergotrate which produce cramps and greatly increased uterine activity, as was shown by the recordings. The decrease in uterine motility and relief from cramps, following the administration of progesterone, indicates a direct effect on uterine contractility and may be attributed to changes in the character of the contractions. If electrical correlates of dysmenorrhea, recorded as increased motility in the uterus, can be further established, then perhaps a criterion for the selection for those patients capable of being relieved of premenstrual pain may be available. The bio-electric findings confirm and may shed some light on the statement of Sevringhaus<sup>15</sup> that certain types of functional dysmenorrhea are favorably influenced by the injection of progesterone, but the mechanism by which the effect is obtained is little understood at the present time. Further studies of the relationships between uterine hypermotility and dysmenorrhea by means of electrical recording is indicated, since Falls and others<sup>16</sup> have shown that the introduction of a hydrostatic bag into the uterus of a seventh-day parturient patient recorded a decrease in uterine tone and motility, following the injection of progesterone.

The increased activity of the uterus to injections of pituitrin occurring in a constant and repetitive character throughout all phases of the cycle, confirms the findings of Kurzrok and others,<sup>3</sup> and Morse and Rubin.<sup>17</sup> The effects as recorded are significant, appearing within fifteen minutes after the injection, and producing severe uterine cramps which coincided with wide voltage swings. Ergotrate caused a more intense and increased motility of the uterus and more severe cramps, the response occurring four to five minutes after intravenous injections.

The response of the uterus during spontaneous menopause to estradiol benzoate suggests the action of the ovaries on uterine motility. The increased activity resulting from estradiol injections within thirty minutes following administration of the hormone indicates that it is absorbed with comparative rapidity. The effect of estradiol on the myometrium is one of stimulation, since an increased uterine contractility was noted in all the patients receiving this hormone.

It is not possible on the basis of the present experiments to explain the action of the sex hormones on the uterus. The technique described

above offers a possible means of analyzing the relationships between uterine physiology and both hormones and other chemical agents. The results obtained indicate a specific hormonal and chemical effect upon the uterine musculature of the cervix.

### CONCLUSION

The studies here reported show that records of the slowly changing standing potential between the dorsal and ventral lips of the human cervix can be correlated with phasic changes during menstruation and with administration of sex hormones and other chemical agents. Moreover, the procedure is relatively simple, can be carried out on the intact organism, and introduces a minimum of disturbance to the physiology of the patient.

### REFERENCES

- (1) *Dickinson, Robert L.*: Human Sex Anatomy, Baltimore, 1933, Williams and Wilkins. (2) *Knaus, H.*: Zentralbl. f. Gynäk. 53: 2193, 1929. (3) *Kurzrok, R., Wiesbader, H., Mulinos, M. G., and Watson, B. P.*: Endocrinology 21: 335, 1937. (4) *Moir, C.*: Brit. M. J. 1: 1022, 1932. (5) *Adair, F. L., and Davis, M. E.*: AM. J. OBST. & GYNEC. 27: 383, 1934. (6) *Theilhaber, A.*: Monatschr. f. Geburtsh. u. Gynäk. 31: 727, 1910. (7) *Bode*: Zentralbl. f. Gynäk. 553: 2887, 1931. (8) *Veit, J.*: Ibid. 36: 161, 1912. (9) *Falk, H. C., and Nahon, R.*: AM. J. OBST. & GYNEC. 30: 403, 1935. (10) *Jacobson, E., Lackner, J. E., and Sinykin, M. B.*: Ibid. 38: 1008, 1939. (11) *Vozza, F.*: Ann. di ostet. e ginec. 55: 603, 1933. (12) *Burr, H. S., Lane, T. C., and Nims, L. F.*: Yale J. Biol. & Med. 9: 65, 1936. (13) *Fenning, E. H., and Browne, J. S. L.*: Endocrinology 21: 722, 1937. (14) *Wilson, L., and Kurzrok, R.*: Ibid. 23: 79, 1938. (15) *Sevringhaus, E. L.*: Endocrine Theory in Clinical Practice, Chicago, 1938, Chicago Medical Book Co., p. 158. (16) *Falls, F. H., Lackner, J. E., and Kronin, L.*: J. A. M. A. 106: 271, 1936. (17) *Morse, A. H., and Rubin, I. C.*: Surg., Gynec. & Obst. 71: 620, 1940.

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**Mahoney, J. P., and Chamberlain, John W.**: Hydrometrocolpos in Infancy, J. Pediat. 17: 772, 1940.

This paper deals specifically with a condition infrequently seen in infants, namely the accumulation of abnormally free secretion of fluid above an atretic occlusion in the vagina. The resulting palpable, perhaps visible, abdominal tumor can be identified before operation by a procedure suggested by the writers.

On the basis of four personally observed cases, described in detail, and of a study of the literature, the writers are able to draw several noteworthy conclusions. The obstruction may be due to an imperforate hymen but probably usually is due to arrested development and failure of perforation of the vagina analogous to imperforate anus. Hematocolpos, with symptoms starting only after puberty, suggests that the chief factor in causing discomfort in hydrometrocolpos is the accumulation of thin, mucinous, cloudy fluid, chiefly in the uterus. A simple procedure allows early correct diagnosis. If in the presence of a palpable tumor in lower abdomen of an infant a cystic bulge is palpable in the vagina, a needle puncture is made, and after aspiration of turbid fluid, approximately 20 c.c. of diodrast are injected. Thus can be ruled out other types of tumors requiring laparotomy. Some of the presenting symptoms might be due to compression or obstruction in either urinary or intestinal tract.

HUGO EHRENFEST.

# BACTERIOLOGIC CHARACTERISTICS OF ANAEROBIC STREPTOCOCCI RECOVERED FROM POST-PARTUM PATIENTS\*

WITH SPECIAL REFERENCE TO THE INITIATION OF INFECTION  
BY THESE ORGANISMS

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WE HAVE been studying anaerobic streptococci for the past three and one-half years at New York University and Bellevue Hospital, our interest primarily being centered on the fact that we, in common with many other observers, have noted that this organism is frequently responsible for puerperal infection. Time does not permit a lengthy historic review of the bacteriologic work performed heretofore in an attempt to learn and evaluate certain of the characteristics of the organism. Suffice it to say that classification of this streptococcus has been attempted on morphologic characteristics, coupled with certain demonstrable alterations on the substrate in which it is cultured and that the consensus of opinion seems to be that it is nonpathogenic for laboratory animals despite its undoubted human pathogenicity.

We proceeded with the work on the anaerobic streptococcus from two hypothetical possibilities. The first of these assumed that a specific type or group of the organisms, having certain recognizable characteristics, was responsible for the human infections because of some particular attribute of virulence not possessed by the majority. This was a logical assumption, since anaerobic streptococci can be isolated from a large percentage of puerperal women, only a small fraction of whom develop infection. The second possibility assumed that most individuals were refractory to infection with the organism and that only a few exhibited specific susceptibility which might be demonstrable by experimental methods.

The first of these possibilities involved the initial classification of the organisms on an arbitrary basis on the chance that strains which had been shown to have caused infection would fall into groups distinct from nonpathogenic strains and consequently attempted classification on morphologic and biochemical reactions was the first line of investigation.

As a result of our investigations, the following facts were noted:

On horse blood agar after forty-eight hours' incubation in the Brown anaerobic jar all strains of anaerobic streptococci have a superficial resemblance. The colo-

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nies are small, round, slightly convex, and grayish white in color. On this medium, there is produced a peculiar and characteristic sweetish foul odor. In no case was hemolysis noted either immediately or after ninety-six hours, but after storage in the refrigerator for a period of months small zones of hemolysis could be seen surrounding each colony of a few of the strains. Hemolysis, however, did not occur within ninety-six hours on subculture of these colonies.

In cooked meat medium under vaseline the organisms required forty-eight hours for good growth at the end of which time they were seen to have grown best around the meat in the bottom of the tube.

All strains with the exception of four were obligate anaerobes and could not be adapted to growth under aerobic conditions. Four strains after six to eight months' artificial cultivation exhibited tolerance to aerobiosis and grew well on horse blood agar (Table I). Seven of 26 strains produced gas and 15 of the 26 strains produced a very foul, putrid odor (Table II).

TABLE I. COLONY DESCRIPTION

ROUND, CONVEX, TRANSLUCENT, GLOSSY, GRAYISH WHITE STRAINS	ROUND, SLIGHTLY CONVEX, TRANSLUCENT, LIGHTER AT EDGES, DULL, GRAYISH WHITE STRAINS	ROUND, PUNCTIFORM, TRANSPARENT, EFFUSE, GRAY STRAINS
Hod	Odu	Mur
Gow	Odo	Hub
Cob	TerA	Kud
Syl II	TerB	Syl
Tam*	Kas	
Dre	Ase	
Fer	Dau	
Def	Eff	
Mik	Lin	
Rze*		
Myi*		
Myt		
Len*		
13	9	4

\*Indicates strains which later exhibited tolerance to aerobic conditions.

TABLE II. GAS AND ODOR PRODUCTION 96 HOUR INCUBATION

FOUL ODOR ALONE	GAS ALONE	GAS AND FOUL ODOR	NO GAS OR ODOR
Hub	Mik	Odu	Mur
Hod	Def	Cob	Syl II
TerA		Syl	Gow
TerB		Dau	Eff
Myi		Kud	Lin
Ase			Rze
Kas			Fer
Myt			Odo
Tam			Dre
Len			
10	2	5	9

Microscopically the organisms appeared as small cocci in chains of three to eight elements. The individual elements were somewhat smaller than staphylococci or hemolytic streptococci. In occasional cultures, more especially in older cultures, diphtheroid forms could be noted. The Gram reaction was variable, and while most of the organisms when freshly cultured were gram-positive, gram-negative forms were not at all uncommon.

It was immediately apparent that morphologic differences were not sufficiently marked to make identification simple, and further, that organisms isolated from human infections did not fall into a specific

group on morphologic criteria. This being the case, further investigation of 26 strains was undertaken as to the properties of the organisms in respect to: (1) the fermentation of various sugars; (2) the quantity of acid produced in media containing sugar; (3) the inhibitory effect of bile; and (4) the ability to hydrolyze sodium hippurate. The results of these studies, each of which was repeated many times, are summarized in Table III.

It will be seen by reference to Table III that clear-cut groupings may be made according to one or another of the criteria employed, but it is also apparent that there is no correlation between grouping by any two of these criteria. The table itself, arranged arbitrarily on the basis of the inhibitory effect of bile, shows three groups of anaerobic streptococci, differing with respect to this inhibition, but these groupings show no uniformity of response to any of the other biochemical tests employed.

Because classification along morphologic and biochemical lines was manifestly unsatisfactory, we determined to attempt to demonstrate more fundamental differences which might exist, by means of serologic technique. It was found possible by inoculation of rabbits with killed cultures, to prepare sera with a moderately high precipitin titer against the strain employed. Twenty-four sera thus prepared were tested against hydrochloric acid extracts of each of the strains with the results which are presented in Table IV. The numbers represent the sum of an arbitrary approximation of the strength of the reaction in three dilutions of extract.

Reference to Table IV shows that in the group of organisms investigated there are many which cross-react, indicating that these organisms possess at least one antigen in common with the organisms used to produce the antiserum. Without going into the immunologic implications too deeply, it has been demonstrated that there are several antigens in the anaerobic streptococcus, one of which might be called type specific, whereas others indicate broader group relationships. It may be possible with further refinement of immunologic technique to classify the anaerobic streptococci according to their antigenic structure. At the same time it becomes increasingly clear that while such a classification may be possible, its practical value is open to question since, with the work already done, no cross-reactions are found to exist among those organisms which have been shown conclusively to be responsible for disease in human beings. Thus four strains isolated in pure culture from the blood of patients exhibiting the typical clinical picture of anaerobic streptococcal septicemia failed to exhibit any immunologic relationships.

It has been demonstrated that there is a relationship of certain strains of anaerobic streptococci to beta hemolytic streptococci of Groups A, B, and C. This relationship was found to exist in 14 of 24 strains tested but no comment in reference to its significance can be made at this time. The greatest number of cross-reactions were noted with Group C hemolytic streptococci, 8 of the 14 strains reacting with sera against this organism.

TABLE III

STRAIN	FINAL PH IN GLUCOSE	GROWTH IN BILE*		FERMENTATION OF		HYDROL- YSIS OF SOD. HIP- PURATE	FERMENTATION OF†					
		10 PER CENT	40 PER CENT	TREHA- LOSE	SOR- BITOL		GLUCO.	MALTO.	LACT.	INUL.	MAN.	SAL.
Syl	4.90	++	++	-	-	+	A	A	A	A	-	-
Tam	4.95	++++	++++	-	-	+	A	A	(A)	(A)	-	-
Eff	6.90	++	++	-	-	+	A	-	-	-	-	A
Hub	6.22	++++	+	-	-	+	-	-	-	-	-	-
Lin	6.71	++++	+	-	-	+	-	-	-	-	-	A
Kas	7.01	++++	±	-	-	+	-	-	-	-	-	-
Gow	6.69	++++	±	-	-	+	-	-	-	-	-	-
Dau	6.89	++	±	-	-	+	-	-	-	-	-	-
Mik	4.95	++	±	-	-	+	(A)	-	-	-	(-)	-
Mur	6.83	++	±	-	-	+	-	-	-	-	-	-
Syl II	6.95	++	±	-	-	+	-	-	-	-	-	A
Odo	6.25	++++	±	-	-	+	-	-	-	-	-	-
Hod	6.82	++++	±	-	-	+	-	-	-	-	-	-
Ase	7.10	++++	±	-	-	+	-	-	-	-	-	-
Rze	6.05	++	-	-	-	+	-	-	-	-	-	-
Len	5.10	++	-	-	-	+	A	A	(-)	(-)	-	-
Fer		++	-	-	-	+	-	-	-	-	-	A
Myt	7.19	±	-	-	-	+	-	-	-	-	-	-
Odu	6.10	±	-	-	-	+	-	-	-	-	-	-
Myi	5.60	±	-	-	-	+	-	-	-	-	-	A
TerA	6.69	-	-	-	-	+	-	-	-	-	-	-
TerB	6.36	-	-	-	-	+	-	-	-	-	-	-
Kud	7.16	-	-	-	-	+	-	-	-	-	-	-
Dre	7.20	-	-	-	-	+	-	-	-	-	-	-
Def	7.49	-	-	-	-	+	(-)	(-)	(-)	(-)	(-)	(-)
Cob	5.50	-	-	-	-	+	(-)	(-)	(-)	(-)	(-)	(-)

\*++++ to - indicates degrees of growth.

†A, acid; (A), acid and gas; - no fermentation; (-) gas but no acid.





On the whole, the investigation of these organisms from the viewpoint that there exists a uniform group of potential pathogens in a larger group of strict saprophytes, has been disappointing. This being the case, it was decided to investigate the possibility that any of the indigenous strains might incite disease under specific conditions. In such an investigation factors altering resistance and favoring growth of the organisms had to be considered. Early in the study it was found that the normal aerobiosis of tissue favored the rapid destruction and phagocytosis of anaerobic streptococci. In most cases of puerperal infection, one is justified in assuming that necrotic remnants of tissue remain in the uterus following parturition, and it was thought possible that such particles of tissue might well serve as a nidus for the growth and dissemination of anaerobic streptococci. Inoculation of these organisms, however, into the uteri of recently delivered rabbits caused no appreciable ill-effects. However, by inoculating fresh cultures of anaerobic streptococci intratesticularly after ligation of the blood supply to the testis, it was found that organisms could be recovered from the necrotic testis seven to fourteen days after inoculation and, further, that within seven days anaerobic streptococci could be demonstrated in the blood stream. This fact is apparently more interesting than significant, since none of these animals exhibited any signs of illness nor did any of them die. Passage of one strain by intratesticular inoculation through 8 successive guinea pigs failed to heighten its virulence for these animals. Attempts to produce infection in guinea pigs, mice, rats, rabbits, and monkeys by a variety of routes of inoculation likewise met with failure. The addition of mucin, reducing substances, and foreign tissue to cultures of the organisms prior to inoculation into animals had no apparent effect.

The fact that anaerobic streptococci are nonpathogenic for laboratory animals and, indeed, for most human beings is not a newly discovered one. It has been noted by almost all investigators of the problem, and it thus seemed probable or at least possible that some serum factor, lethal for the organisms, was present in the common laboratory animals and perhaps in the majority of human beings. This theory would account for the relatively low incidence of infection even in the face of the high percentage of women harboring the organism in the vagina. Further, it had been shown previously by Colebrook and Hare<sup>1</sup> that anaerobic streptococci die rapidly in serum or blood clot. With these considerations in mind, the investigation of a serum factor influencing resistance seemed a profitable line of endeavor.

The study of these factors of resistance is still in its early stage and consequently it is not proper to draw final conclusions, but a few points may be mentioned. It seems fairly certain that phagocytosis alone does not play a major role, since the serum of normal persons is able to activate white cells to phagocytize the organisms to an extent neither greater nor lesser than the serum from persons suffering from severe anaerobic streptococcal septicemia. One should expect, if lack of phagocytic power alone determined susceptibility, that serum from a patient in the early stages of such an infection would show a reduced activating power, which theoretically at least would increase

when and if recovery ensued. This has not been found to be the case, for we have noted both greater and lesser degrees of phagocytosis for the same organism in what appears to be a wholly erratic manner with no apparent relationship to the stage of the disease. In all fairness, it must be mentioned that the study of the phenomenon of phagocytosis is one beset with many difficulties, owing to this wide variation even in normal subjects from day to day.

The question as to whether or not a bactericidal factor for the anaerobic streptococcus is present in the sera of human beings or animals is another one which has not fully been answered. From the work so far performed, it is a fact that exposure to certain sera for lengths of time varying from twenty-four to forty-eight hours kills the organisms so that subculture of the serum-organism mixture is no longer possible. In one instance recently under our observation, the serum from a patient ill with anaerobic streptococcal septicemia for over forty days, failed to kill a fresh culture of the organisms isolated from the patient's blood stream but did destroy other cultures of anaerobic streptococci serologically unrelated to this organism. In this instance, of course, the evidence points to a specifically virulent strain of the organism rather than to a lack of any nonspecific serum factor. Again, we would like to state that this work is not completed and that, therefore, conclusions are not justified.

It is interesting to note that recovery from anaerobic streptococcal septicemia does not result in the presence of demonstrable antibodies in the patient's serum. In all the cases which have been under study, no precipitins or agglutinins against the organism isolated from the blood stream of the patient could be found even after rather long periods of illness. This was true in spite of the fact that there could be no question as to the specificity of the organism causing the disease, for in many cases it was isolated repeatedly from the blood stream. In a few cases, however, a specific hypersensitivity could be demonstrated late in convalescence by means of skin tests with extracts of the organism recovered from the patient.

It follows from the results described above that the mechanism of infection with the anaerobic streptococcus depends more upon individual patient susceptibility than upon a specific group or type of virulent organism and that recovery proceeds in a manner not completely understood at the present time. Until a greater amount of experimental work is performed, however, no final conclusions are permissible.

#### REFERENCES

- (1) Colebrook, L., and Hare, R.: *J. Obst. & Gynaec. Brit. Emp.* 40: 609, 1933.
- (2) Stone, Melvin, L.: *J. Bact.* 39: 559, 1940.

## RUPTURED UTERUS

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**R**UPTURED uterus, although of infrequent occurrence, ranks first among obstetric complications in its disastrous effect upon both mother and baby. The infrequency of its occurrence in itself adds to the seriousness of the situation, because very few obstetricians observe enough cases to become proficient in diagnosis and treatment. Exceedingly important is the fact that the possibility of ruptured uterus must always be kept in mind even though labor and delivery seem to be pursuing a normal course. The case in which the typical textbook set of symptoms and signs occur probably will not often be overlooked. However it is the unusual variation of this distressing obstetric problem which all too frequently is not recognized until precious and irretrievable time has been lost. Diagnosis of all cases must be prompt and treatment instituted immediately and effectively if the appalling death rate of ruptured uterus is ever to be reduced.

This paper presents a survey of a larger group of cases with the object of re-familiarizing both general practitioner and obstetrician with the various features of this infrequent but nevertheless tragic condition.

In an unusually active practice of forty years, DeLee attended 19 patients with complete rupture, 11 of whom died; and 19 patients with incomplete tear, 3 of whom died. At St. Luke's Hospital, Cleveland, there occurred 12 cases of uterine rupture in 17,793 deliveries or an incidence of 1 in 1,483 deliveries, 5 of whom died.

The data herein presented and conclusions arrived at are the result of an analytical survey of 45 cases of ruptured uteri, only 3 of which have been previously reported (Woodward). Twelve of these cases occurred at St. Luke's Hospital. The remaining 33 cases represent the total number of uterine ruptures occurring during the past five years in 41 of the 47 member hospitals of The Hospital Obstetric Society of Ohio.

Each case report is the result of a detailed personal communication with the physician in charge of the case. At this point I wish to express my deep appreciation to those physicians who were kind enough to cooperate with me in this study.

### AGE INCIDENCE

In the patients studied, the age span varied from 19 to 48 years, with an average age of 31 years. It is evident that the possibility of uterine rupture must be considered in every gravida regardless of age.

### PARITY

The number of pregnancies preceding the one in which rupture occurred varied from none to fifteen.

TABLE I. AGE INCIDENCE

Under 20	2	35 to 40	8
20 to 30	7	40 to 45	5
25 to 30	11	45 to 50	1
30 to 35	11		

TABLE II. PARITY

Parity	0	i	ii	iii	iv	v	vi	vii	viii	xi	xv
Number of cases	2	14	8	4	5	5	1	3	1	1	1

In 2 patients, uterine rupture occurred during the first pregnancy, and in both was the result of trauma caused by internal podalic version. Fourteen patients had only one previous pregnancy and 9 of these were patients in whom previous cesarean section had been performed. Eight patients had two preceding pregnancies, and of these, five had been subjected to a previous section. There were a total of 18 cases in which cesarean section had been performed prior to the pregnancy in which rupture occurred (Table III). It is, therefore, apparent that the most frequent cause of uterine rupture in patients of lesser gravidity is previous cesarean section; whereas spontaneous rupture is the most frequent cause in patients of greater gravidity.

#### LENGTH OF LABOR

The length of labor preceding the rupture varied considerably, from no labor to 96 hours. In 9 patients rupture occurred before the onset of labor. There were 30 patients with labor of less than ten hours and 15 patients with labor more than ten hours. The average length of labor in the patients where previous section had been performed was nine hours, as compared with eighteen hours of labor in the patients where section had not been performed.

If we exclude all cases occurring before the onset of labor or during the actual delivery, and only include the cases occurring during labor, we find that the average length of labor before rupture is twelve hours.

#### CAUSE OF UTERINE RUPTURE

Of paramount importance, of course, is the reason why uterine tear occurs. Only by careful consideration of the causative factors involved will we be able to determine in the future how best to avoid rupture of the uterus.

TABLE III. CAUSE OF RUPTURE

	CASES	SURVIVED	DIED
1. Previous cesarean section	18	16	2
2. Cause not definitely determined, perhaps due to myometrial changes	9	3	6
3. Internal podalic version	5	3	2
4. Uncorrected transverse presentation	4	2	2
5. Obstructed labor			
a. Cephalopelvic disproportion	4	1	3
b. Obstructing ovarian cyst	2	1	1
6. Previous pelvic peritonitis	1	1	0
7. Eclamptic convulsion	1	0	1
8. Previous curettage	1	1	0

At this point, we might consider which of these cases possibly could have been prevented. Attendance at each case would be the only accurate way of determining which patient could have been managed more judiciously, so that rupture would not have occurred. However, from the evidence at hand, we can say that most probably the ruptures represented in items 3, 4, and 5, that is 15 cases (33

per cent), could have been prevented by more accurate diagnosis and more efficient treatment of the primary obstetric condition.

Internal podalic version is a very useful maneuver. However great care must be taken in its performance, and it should never be used if any of the well known contraindications are present. Transverse presentation can and must be recognized early if it is to be adequately treated. A more liberal use of the x-ray whenever any doubt exists would bring these cases to light soon enough to institute the proper corrective measures. Also in several of the cases where the indication for the previous cesarean section was cephalopelvic disproportion, the patient should not have been permitted to labor more than a few hours. Whenever a previous section is done for cephalopelvic disproportion, termination of succeeding pregnancies by cesarean section would be the method of choice, unless the baby is much smaller than the previous one. At any rate, if labor is permitted, all preparations should be made to promptly treat a threatened or actual rupture, including readily available blood donors.

#### ANALYSIS OF RUPTURED UTERI WITH PREVIOUS CESAREAN SECTION

Table IV is a presentation of the salient features occurring in the cases of uterine rupture following previous cesarean section. Of the 45 cases in this entire survey, 18, or 40 per cent, were in patients previously subjected to section. Nine of the sections were performed because of disproportion, 2 each because of placenta previa and ablatio placentae, 3 as treatment for eclampsia, and 1 because of reported interlocked twins.

Two methods of treatment were used, supracervical hysterectomy and suturing of the lacerated uterus. Of the 9 patients treated by hysterectomy, 1 died and 1 had a stormy convalescence; the remainder recovered uneventfully. Of the 8 patients treated by suturing of the uterine tear, all recovered, but one had a stormy convalescence. One patient died before treatment could be instituted; however, death was probably due to a pre-existing pneumonia rather than from the ruptured uterus.

TABLE IV. RUPTURED UTERI FOLLOWING PREVIOUS CESAREAN SECTION

CASE	INDICATION FOR SECTION	LENGTH OF LABOR	TIME OF RUPTURE		TREATMENT	RESULT	
			BE-FORE LABOR	DUR-ING LABOR		MOTHER	BABY
1	Disproportion	4 hr.		x	Suture	Survived	Dead
2	Disproportion	52 hr.		x	Suture	Survived	Survived
3	Disproportion	10 hr.		x	Suture	Stormy recovery	Dead
4	Disproportion	36 hr. (6 mo.)		x	Suture	Survived	Dead
5	Disproportion	0 (7 mo.)	x		Hysterectomy	Survived	Dead
6	Disproportion	0	x		Suture	Survived	Dead
7	Disproportion	5 hr.		x	Suture	Survived	Dead
8	Disproportion	1 hr.		x	Hysterectomy	Survived	Survived
9	Disproportion	14 hr.		x	Hysterectomy	Survived	Dead
10	Placenta previa	4 hr.		x	Hysterectomy	Survived	Dead
11	Placenta previa	0	x		Hysterectomy	Survived	Survived
12	Ablatio placentae	0	x		Suture	Survived	Survived
13	Ablatio placentae (cervical section)	18 hr.		x	Suture	Survived	Survived
14	Eclampsia	0	x		Hysterectomy	Stormy recovery	Dead
15	Eclampsia	10 hr.		x	Hysterectomy	Survived	Dead
16	Eclampsia (cervical section)	3 hr.		x	Hysterectomy	Survived	Dead
17	Interlocked twins	3 hr.		x	Hysterectomy	Died	Dead
18	Indication unknown	0	x		No time	Died	Dead

From the foregoing it would seem that the treatment of choice is suture of the torn uterus, although both methods of treatment gave nearly comparable results. In deciding upon which form of treatment to use, several factors must be borne in mind. If the patient has no living children or only one child, it probably would be best to try to preserve the uterus; however, the possibility of rupture must be borne in mind in the event of future pregnancy. If a pregnancy does occur, delivery should be by elective section and tubal sterilization or hysterectomy about two weeks before the estimated date of confinement. Case 3 (Table IV) illustrates this point. This patient had a ruptured uterus in 1936, following a previous cesarean section. Treatment was by suture of the laceration. Then in 1939 the patient again became pregnant, and this time she was delivered by elective section and hysterectomy.

Of the 18 patients having had a previous cesarean section, 6 suffered rupture of the uterus before the onset of labor; while of the 27 nonsection cases, only 3 sustained uterine rupture before labor commenced. Uterine tear is much more likely to occur before the onset of labor in patients subjected to previous cesarean section than in those not having had a previous section.

TABLE V. TIME OF RUPTURE

	ENTIRE SERIES	PREVIOUS SECTION CASES	NONSECTION CASES
Before labor	9	6	3
During labor	26	12	14
During delivery	10	0	10

The dictum "Once a cesarean always a cesarean" even if accepted by all obstetricians would not be sufficient to protect every previously sectioned patient from the hazards of uterine rupture. It is imperative that every gravida with a history of previous section be very closely watched at all times during her pregnancy, and especially during the last two or three months, for evidence of impending or even actual rupture. Complaints of vague abdominal pain and tenderness should not be dismissed without a careful examination and frequent observation. Typing and cross-matching of blood donors should be done not later than the beginning of the third trimester, so that transfusions can be performed without delay if uterine rupture does occur.

The maternal mortality rate in the group of patients having had a previous section was 11 per cent. The fetal mortality rate in this group was 72 per cent. Various other investigators have found the maternal mortality rate to vary from 13 per cent (Asa B. Davis) to 50 per cent (Weber).

The incidence of uterine rupture following classical section varies from 2 per cent (Kerr) to 6 per cent (Audebert). Gelle, in 1932, reviewed all available cases of cervical section and estimated that the incidence of uterine rupture was 0.25 per cent or one-sixteenth of that found following the classical section. The present series includes 2 cases of rupture, following a previous cervical section; both patients recovered uneventfully.

Shock is the most prominent and the most serious manifestation of uterine rupture. However, shock was present in only 2 of the 18 cases where previous section had been done, while it was a prominent symptom in 23 of the 27 nonsection cases. This explains the low mortality rate in the group of previous section cases.

The obstetrician who decides in favor of vaginal delivery in the management of a patient having had a previous section (disproportion not being a factor), assumes less of a maternal risk than if he routinely re-sectioned all patients. The average incidence of uterine tear following previous classical section is about 4 per cent, i.e., 4 patients out of every hundred would suffer uterine rupture if they were all permitted to deliver vaginally. Of these 4, only 11 per cent, or 0.36 patient, would die. Whereas, if the entire hundred patients were routinely re-sectioned, the basic mortality rate would be from 1 to 2 per cent (Skeel and Jordan).

## UTERINE RUPTURE OCCURRING DURING DELIVERY

There were 10 cases in which rupture took place during the actual delivery. As we can see (Table VI) internal podalic version was the cause of 60 per cent of the uterine tears in this group, with a mortality rate of 50 per cent.

TABLE VI. TYPE OF DELIVERY

	CASES	SURVIVED	DIED
Internal podalic version	6	3	3
Spontaneous delivery	3	2	1
Breech extraction	1	0	1

## LOCATION OF RUPTURE

Table VII shows that laceration of the posterior wall of the uterus was the most disastrous, causing a 100 per cent mortality in this series. Lacerations of the lower uterine segment caused the next highest death rate, 5 of the 9 patients dying. A distinct danger of lower uterine segment rupture is involvement of the bladder. Left lateral ruptures were the next most serious, with a 50 per cent maternal mortality.

TABLE VII. LOCATION OF RUPTURE

	CASES	SURVIVED	DIED
1. Location not stated	2	1	1
2. Previous classical scar	16	14	2
3. Previous cervical section scar	2	2	0
4. Lower uterine segment	9	4	5
5. Posterior wall	4	0	4
6. Left lateral	6	3	3
7. Right lateral	3	2	1
8. Bilateral	1	0	1
9. Anterior wall	2	1	1

## TYPE OF RUPTURE

The two recognized types are the complete and incomplete. The incomplete variety is characterized by the fact that the endometrium and myometrium are involved, but the uterine peritoneum remains intact. Whereas, in the complete type, the peritoneum is also lacerated, thus making a direct communication between the interior of the uterus and the general peritoneal cavity. Peritonitis is of more frequent occurrence in the complete type.

In this series there were 38 complete uterine ruptures and 7 incomplete ruptures. There is little doubt that there are probably more incomplete ruptures than are recognized. It is a good idea to explore carefully the interior of every uterus where there has been a difficult instrumental delivery or where internal manipulation has been performed. Internal uterine exploration under aseptic conditions bears very little risk, and certainly far less risk than a neglected incomplete rupture. Table VIII illustrates the greater risk of complete rupture.

TABLE VIII. TYPE OF RUPTURE

	CASES	SURVIVED	DIED
Complete rupture	38	22	16
Incomplete rupture	7	6	1

Of the 22 patients with complete rupture that survived, 6 had a stormy convalescence due to peritonitis. The 6 surviving patients with incomplete rupture recovered uneventfully.

A study of the fate of the infant also reveals the more devastating effect of the complete type of rupture (Table IX).



TABLE IX. TYPE OF RUPTURE

	CASES	SURVIVED	DIED
Complete rupture	38	6	32
Incomplete rupture	7	4	3

METHOD OF TREATMENT IN CASES WHERE PREVIOUS SECTION  
HAD NOT BEEN PERFORMED

A study of Table X reveals that the 7 patients in the first group died of hemorrhage and shock before effective treatment could be instituted. However, in several of these cases, the diagnosis was not made until it was too late. Earlier diagnosis might have saved these patients.

Supracervical hysterectomy gave the best results. Most of the uteri were lacerated in such a manner that removal of the uterus was the only feasible method of treatment. Two patients were treated by suturing of the laceration; one patient died of paralytic ileus and the other died of peritonitis which apparently was present at the time the laparotomy was done.

TABLE X. TREATMENT OF NONSECTIONED RUPTURED UTERI

	CASES	RECOVERED	DIED
1. No time for treatment	7	0	7
2. Supracervical hysterectomy	17	12	5
3. Laceration sutured	2	0	2
4. Uterine arteries clamped vaginally	1	0	1

IMMEDIATE CAUSE OF DEATH

By far the most frequent immediate cause of death was hemorrhage and shock. Most of these patients bled so profusely intra-abdominally that death occurred before treatment could be instituted, or, if operation was performed, death occurred soon afterward.

Nine patients died before laparotomy could be performed. Of these, in only one case was there time for a blood transfusion. Five patients died during or shortly after operation. Three of these had transfusion.

Nineteen of the 28 surviving patients had from 1 to 7 transfusions.

MORTALITY

In this series of 45 cases, there were 17 maternal deaths and 31 fetal deaths, that is, a death rate of 37 per cent and 69 per cent, respectively.

TABLE XII. MORTALITY RATE

	NUMBER OF CASES	MATERNAL DEATHS	FETAL DEATHS
Entire series	45	17 (37%)	31 (69%)
Previous section cases	18	2 (11%)	13 (72%)
Nonsection cases	27	15 (55%)	18 (66%)

The death rate occurring in the present series compares favorably with that of other recent investigators. Asa B. Davis, in 1927, had a total maternal death rate of 56.6 per cent, and a previous section mortality rate of 12.5 per cent. McNeile and McBurney, in 1935, had a maternal death rate of 20 per cent in previous section cases and 90 per cent in nonsection cases. Davis found a fetal death rate of 80 per cent in section and nonsection cases alike.

SUMMARY

1. An analytical survey of 45 cases of uterine rupture is herein presented.

2. The most frequent cause of rupture of the uterus was previous cesarean section. The trauma of internal podalic version and uncorrected transverse presentation also were prominent causative factors.

3. Supracervical hysterectomy or suture of the uterine laceration gave equally good results in the treatment of cases where rupture followed a previous cesarean section.

4. Supracervical hysterectomy was the treatment of choice in the non-section cases of uterine rupture.

5. There is a definite danger of uterine rupture before the onset of labor, particularly in patients where previous cesarean section had been performed.

6. Internal podalic version was responsible for 60 per cent of the uterine ruptures occurring during the time of delivery.

7. Complete rupture of the uterus is far more serious than the incomplete variety.

8. Hemorrhage and shock was the most common immediate cause of death.

9. The maternal mortality rate for the entire series was 37 per cent; total fetal mortality rate was 69 per cent.

#### REFERENCES

- DeLee, J. B.*: Principles and Practice of Obstetrics, ed. 7, Philadelphia, W. B. Saunders Co., p. 859. *Davis, Asa B.*: AM. J. OBST. & GYNEC. 13: 522, 1927. *Weber, G. H.*: Illinois M. J. 47: 39, 1925. *Kerr, McIntyre, and Hendry*: Brit. M. J. 1: 1093, 1924. *Audebert, J. L.*: Gynec. et obst. 7: 487, 1923. *McNeile, L., and McBurney, R.*: Calif. & West. Med. 42: 73, 1935. *Skeel, A. J., and Jordan, F. F.*: AM. J. OBST. & GYNEC. 23: 172, 1932. *Gelle, P.*: Bull. Soc. d'obst. et gynec. 21: 62, 1932. *Woodward, H. L.*: J. Med. 20: 106, 1939.

10515 CARNEGIE AVENUE

## TREATMENT OF MENSTRUAL DISORDERS WITH PREGNANT MARES' SERUM

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PREGNANT mares' serum was shown by Cole and Hart<sup>1</sup> to possess a powerful stimulating effect on the ovaries of the immature rat, producing ovulation and corpus luteum formation. Evans<sup>2</sup> and Reichert,<sup>3</sup> in their studies on hypophysectomized rats, showed the contrast between pregnant mares' serum and chorionic gonadotropin: The pregnant mares' serum is effective in bringing about structural restoration of the female reproductive system, and chorionic gonadotropin is not. Also, pregnant mares' serum is not excreted by the kidney; therefore, the total dose is available for stimulation. Clinical studies on pregnant mares' serum by Bowes<sup>4</sup> and Frank,<sup>5</sup> Davis and Koff,<sup>6</sup> Dodds and his associates,<sup>7</sup> and Kurzrok,<sup>8</sup> gave indifferent or inconclusive results.

While interest in this hormone centered mostly about its use in overcoming sterility, it has been used in all forms of menstrual disturbances with varying success.<sup>9-13</sup>

Because of these conflicting reports, further clinical experiences with this hormone are here recorded. Seventeen patients with menstrual disturbances were treated: 13 suffered from amenorrhea or oligomenorrhea, and 4 had menorrhagia or metromenorrhagia. In 12 of the 17 patients endometrial biopsies were performed with a suction curette and 4 of the remaining 5 were followed with vaginal smears.

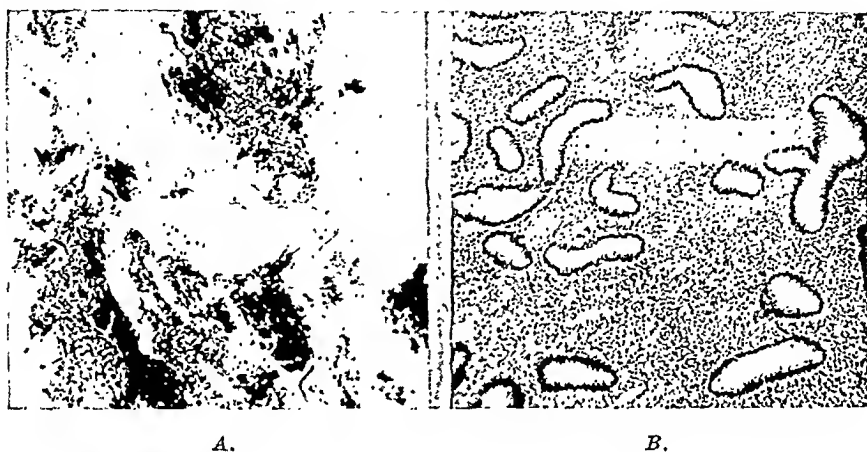


Fig. 1.—A, Endometrial biopsy showing atrophy in patient (H. N.) with amenorrhea of ten months' duration. B, Proliferative phase after 3,000 international units of gonadin. Regular monthly periods have occurred for eight months after treatment discontinued. ( $\times 125$ .)

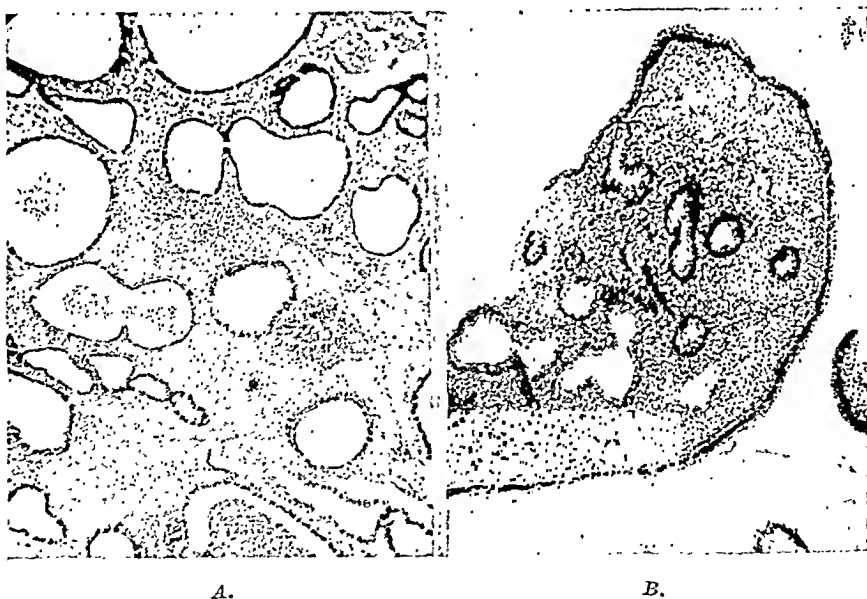


Fig. 2.—A, Endometrial biopsy showing Cullen's hyperplasia in patient (H. M.) with menorrhagia after three weeks' flow. B, Proliferative phase after 3,000 international units of gonadin. Regular three- to seven-day periods have occurred for eight months. ( $\times 125$ .)

Following the suggestion of Novak, patients with amenorrhea and hypomenorrhea were primed with estrone, 16,000 units being the usual preliminary dosage. All of the patients were given a careful physical, endocrinologic and gynecologic examination before pregnant mares' serum was given. All other medication was discontinued. The plan of treatment was to administer 200 international units of pregnant mares'

serum\* intramuscularly, every other day, until 15 injections or 3,000 international units were administered. A rest period followed the injections and, if there was no clinical response, the course was repeated. At intervals, depending upon the progress of the individual patient, endometrial biopsies were again taken. Results of treatment are shown in Table I.

#### DISCUSSION

Seven of the 17 patients with amenorrhea and oligomenorrhea were affected by treatment during the period of injections. When these patients were interviewed eight months later, 2 of the 7 had more than temporary benefit, and in a third patient (A. R.), the four- to six-month menstrual interval was reduced to an interval of three months. Of significant interest is the case of R. Z., aged 17 years, the only case of primary amenorrhea in the series, who failed to show any immediate clinical benefit from treatment, and whose endometrial biopsies showed atrophy before and after treatment. One month after the injections were discontinued she

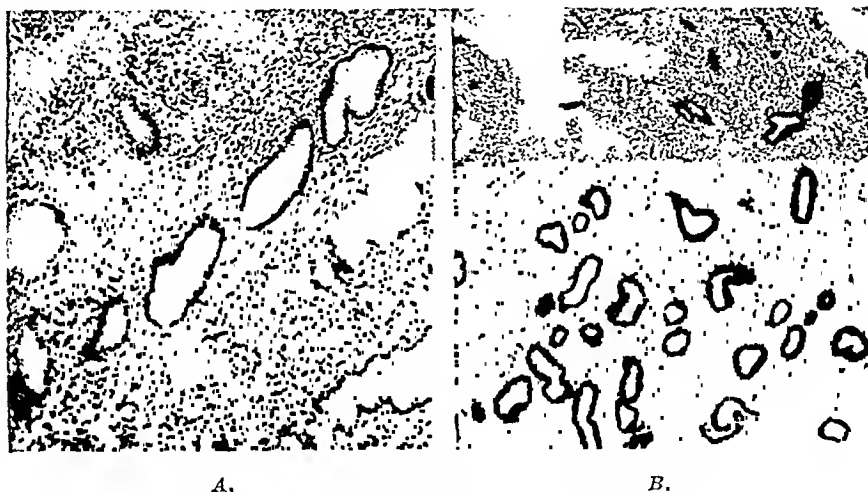


Fig. 3.—A, Endometrial biopsy showing secretory phase in patient (P. M.) with menorrhagia after nine weeks' flow. B, Proliferative phase after 4,200 international units of gonadin. Normal menses occurred for four months; then menorrhagia recurred. ( $\times 125$ .)

menstruated and has continued to have regular monthly periods after eight months. Of further interest is the patient (J. H.) who had acromegaly with an enlarged sella turcica. Since there has been speculation that amenorrhea in acromegaly is the result of suppressed hormone secretion from intrasellar pressure, improvement might have been anticipated from substitutional pituitary therapy.

All four patients with menorrhagia were improved at the time the injections were administered. One of these (H. A.), who had been married for five years without conceiving, became pregnant during the course of treatment. This might be interpreted as an example of induced ovulation, although there was no proof that she was not ovulating prior to treatment. Of the remaining 3 cases of menorrhagia, 2 (H. M. and V. B.) have continued to be benefited eight months after treatment was discontinued.

Three of the 8 patients with amenorrhea and oligomenorrhea, in whom endometrial biopsies were taken, showed changes from an atrophic to a proliferative phase, while no change from the original atrophic pattern was discernible in 4 others. Vaginal smears, in the 3 cases in which they were carefully studied, showed no definite change following the injections. The endometrial picture in the 3 patients with menorrhagia before and after treatment, indicated a regression from the original pattern of hyperplasia to one of proliferation. These changes would seem rather significant in view of the clinical course of these patients.

\*Acknowledgment is made to Mr. Donald Wonder of Cutter Laboratories for a generous supply of gonadin used in these studies.

TABLE I. RÉSUMÉ OF CASES TREATED WITH PREGNANT MARES' SERUM (P. M. S.)

NAME AGE	MENSTRUAL HISTORY	PREVIOUS TREATMENT	AMOUNT P. M. S.	CLINICAL RESULTS		ENDOMETRIUM		VAGINAL SMEARS	
				IMMEDIATE	AFTER 8 MONTHS	BEFORE	AFTER	BEFORE	AFTER
A. B. 29	30-day interval. Scant flow	None	6,000 I.U.	0	0	Atrophy	Atrophy	---	---
R. Z. 17	Primary amenorrhea	Massive doses of estrone	6,000 I.U.	0	Regular periods began 1 mo. after treat- ment	Atrophy	Atrophy	---	---
L. M. 27	Interval of 6 mo.; vary- ing periods of menor- rhagia and metrorrha- gia	Series of estrone and progestin	6,000 I.U.	2 periods at 30-day in- terval	No further period	Atrophy	Atrophy	---	---
J. H. 32	Sudden cessation 3 yr. previous	None	6,000 I.U.	0	0	Atrophy	Atrophy	---	---
C. P. 27	Interval 3-6 mo. 1 day duration past 10 yr.	None	4,200 I.U.	Menstruated	Regular monthly pe- riods	Prolifera- tion	Prolifera- tion	---	---
M. S. 17	Irreg., 3-6 periods a yr. Last menstrual period 3 mo. previous	Desiccated thyroid	6,000 I.U.	Menses more regular during treatment	About same as formerly	Atrophy	Prolifera- tion	---	---
H. N. 20	Irreg. interval 2-3 mo. Last menstrual period 10 mo. previous	None	3,000 I.U.	Menstruated	Regular monthly pe- riods	Atrophy	Prolifera- tion	---	---
M. O. 22	Interval 6 wk. in 4 mo. Scant flow	None	5,400 I.U.	Menses more regular during treatment	Not heard from	Atrophy	Prolifera- tion	---	---

Hypomenorrhea

and

A. R. 18	Interval 4 to 6 mo. Scant flow	None	3,000 I.U.	Menstruated	Regular for 4 mo. No period since	Atrophy	---	---	---
M. A. 20	Fairly regular until last menstrual period 12 mo. previous	Estrone for 9 mo. pe- riod	4,800 I.U.	Vaginal bleeding one time	0	---	Neg.	Pos.	---
P. B. 25	Always irregular. Last menstrual period 15 mo. previous	Thyroid; estrone; gonadotropic hor- mone; urinary go- nadotropin	1,500 I.U.	0	0	---	---	---	---
L. R. 30	Scant flow. Last men- strual period 10 yr. previous	Estrone, two long series	6,000 I.U.	0	0	---	Weak Pos.	Neg.	---
M. P. 33	Irregular past 2 yr. Last menstrual period 3 mo. previous	Estrone	3,800 I.U.	0	0	---	Neg.	Neg.	---
H. M. 30	Flowing 3 wk.	3 dilatation and eu- retage; "shots"	3,000 I.U.	Benefited	3-7 days' dura- tion. Regular	Cullen's hyper- plasia	Prolifera- tion	---	---
P. M. 27	Flowing 9 wk.	Rest; oral medication	4,200 I.U.	Benefited	Improvement for 4 mo. only	Secretory phase	Prolifera- tion	---	---
V. B. 23	Flow lasting 7 to 21 days	2 dilatation and eu- retage	3,000 I.U.	Benefited	Regular, 4-8 days' dura- tion	Cullen's hyperplasia	Prolifera- tion	---	---
H. A. 24	Flowed 2 wk.	None	4,200 I.U.	Pregnant	Full term preg- nancy	Prolifera- tion	---	---	---

Amenorrhoea

Menorrhagia

## SUMMARY

Thirteen patients with amenorrhea and oligomenorrhea were treated with pregnant mares' serum. After eight months' observation, regular monthly periods have continued in 3 of the 13, 1 of the 3 having been a case of primary amenorrhea.

Four patients with menorrhagia were treated; all 4 of whom showed evidence of immediate improvement. One of the 4 became pregnant after a sterile marriage of five years, and has gone on to full term. Two of the remaining 3 have shown continued benefit after eight months.

Endometrial changes in the cases of amenorrhea and oligomenorrhea were inconstant, while in the cases of menorrhagia, the pattern changed from one of hyperplasia to one of proliferation.

The authors wish to express their indebtedness to Dr. Wm. H. Vogt, Sr., Director of the Department of Obstetrics and Gynecology, for his suggestions and invaluable aid in carrying out these studies.

## REFERENCES

- (1) Cole, H. H., and Hart, G. H.: *Am. J. Physiol.* 93: 57, 1930. (2) Evans, H. M.: *West. J. Surg.* 44: 175, 1936. (3) Reichert, F. L.: *Am. J. Physiol.* 157: 1, 1932. (4) Bowes, K.: *Brit. M. J.* 2: 904, 1937. (5) Frank, R. T., Goldberger, M. A., Salmon, U. J., and Felshin, G.: *J. A. M. A.* 109: 1863, 1937. (6) Davis, M. E., and Koff, A. K.: *AM. J. OBST. & GYNEC.* 36: 183, 1938. (7) Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R.: *Nature* 141: 247, 1938. (8) Kurzrok, R.: *The Endocrines in Obstetrics and Gynecology*, Baltimore, 1937, Williams and Wilkins. (9) Kennedy, R. B., and Shelton, C. F.: *J. Michigan M. Soc.* 38: 209, 1939. (10) Gray, L. A.: *South. M. J.* 33: 160, 1940. (11) Siegler, S. L.: *Endocrinology* 27: 387, 1940. (12) Siegler, S. L., and Fein, M. J.: *AM. J. OBST. & GYNEC.* 38: 1021, 1939. (13) Frank, R. T., Goldberger, M. A., and Felshin, G.: *Endocrinology* 27: 381, 1940.

## THE EFFECT OF ORAL ADMINISTRATION OF ALPHA ESTRADIOL AND PREGNENINOLONE UPON THE HUMAN CASTRATE UTERUS

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THE oral effect of estrin,<sup>1</sup> and the combined effect of oral estrin and parenteral progestin<sup>2</sup> upon the human castrate endometrium have been previously demonstrated. This presentation concerns itself with the application of oral estrin (dimenformon)\* and an oral synthetic progestin derivative (pregneninolone)\* upon the endometrium of the human castrate uterus. In addition, an attempt has been made to determine the standard for a human unit of these two ovarian hormones, i.e., the approximate amounts utilized, in milligrams, of crystalline substance during a normal menstrual cycle.

\*We are indebted to Roche-Organon, Inc. for a supply of dimenformon and pregnenolone (progestoral).

## CASE REPORTS AND EXPERIMENTAL PROCEDURES

CASE 1.—F. L.\* white, female, married, aged 37 years, was subjected to bilateral salpingo-oophorectomy for cystic ovaries. Menstruation began at 14, was irregular with occasional intervals of from three to six months, always painful and profuse, at times lasting thirty days. There had been four full-term pregnancies. The castration syndrome developed six months postoperatively. A premedication endometrial biopsy was taken and a scanty amount of tissue obtained; diagnosis of this tissue was atrophic endometrium.

*Bimanual Examination:* Uterus anterior, freely movable; cervix well epithelized and measured  $2\frac{1}{2}$  inches from external os to fundus. Adnexa were not palpable. Vaginal mucosa was pale and dry.

Sept. 26, 1939, to Oct. 7, 1939: Dimenformon, 4 mg. daily, for twelve days.

October 8 to 19: Dimenformon, 6 mg., plus 75 mg. pregneninolone daily for twelve days.

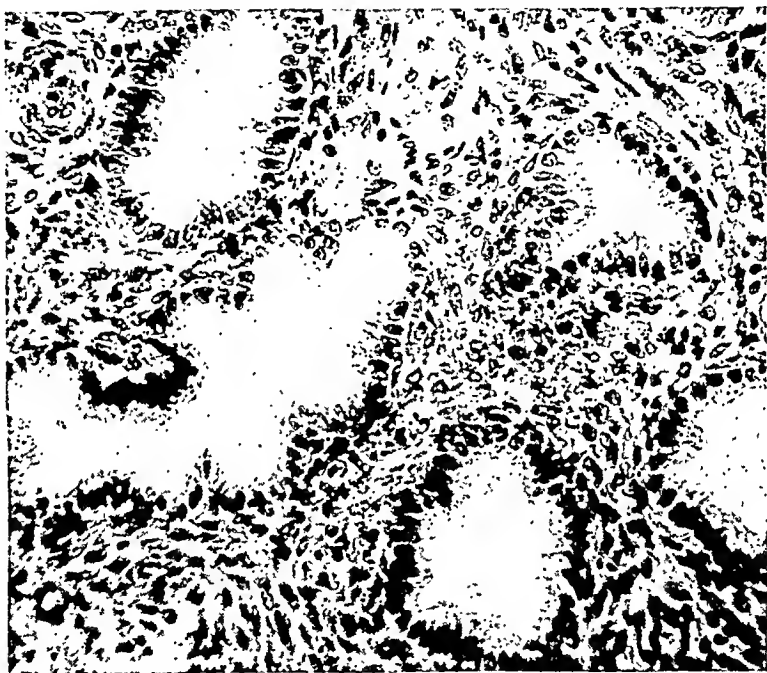


Fig. 1.—Early to midluteal phase produced with 120 mg. of estradiol and 900 mg. of pregneninolone.  $\times 200$ .

October 21: Endometrial biopsy was taken and the diagnosis of an early to midluteal phase of endometrium established (Fig. 1).

October 23 to 26: Bleeding was reported.

The patient noted some increase in libido, flushes disappeared, and the uterine measurement from external os to fundus was  $2\frac{1}{2}$  inches; vaginal secretion was present and the vaginal mucosa was a normal, pinkish hue. For a period of three months she was comfortable, when menopausal symptoms reappeared.

CASE 2.—J. K.\* white, female, married, aged 22 years, was admitted to the Gynecological-Endocrine Clinic, complaining of hot flushes and amenorrhea. Both ovaries had been removed at two previous operations, but the uterus was left in situ with a Crossen suspension. Menstruation began at 15 years of age, of three days' duration, and occurred every thirty days. For two years prior to operation she menstruated every two weeks for ten to eleven days, with a profuse flow and pain.

\*These castrates, now receiving oral estrin and oral pregneninolone, were reported upon in a previous communication<sup>2</sup> after having been given oral estrin and parenteral progestin.



Last period four months previously. Flushes, accompanied by headaches, began soon after operation. Bimanual examination revealed a small uterus which was in anterior position, not freely movable. Adnexa were absent. Uterine measurement, from external os to fundus, was  $2\frac{1}{2}$  inches. A premedication biopsy was taken and a meager amount of endometrium obtained; the tissue was diagnosed as atrophic endometrium.

Dec. 25, 1939, to Jan. 5, 1940: Dimenformon 4 mg. daily for twelve days.

Jan. 6 to 17, 1940: Dimenformon 6 mg. plus 100 mg. pregnenolone daily for twelve days.

January 20: Biopsy taken. Diagnosis: mid- to late luteal phase of the endometrium (Fig. 2).

January 22 to 26: Bleeding was reported. Uterus measured three inches from external os to fundus.

The patient noted no change in libido but described breast stimulation. Flushes completely disappeared during medication.

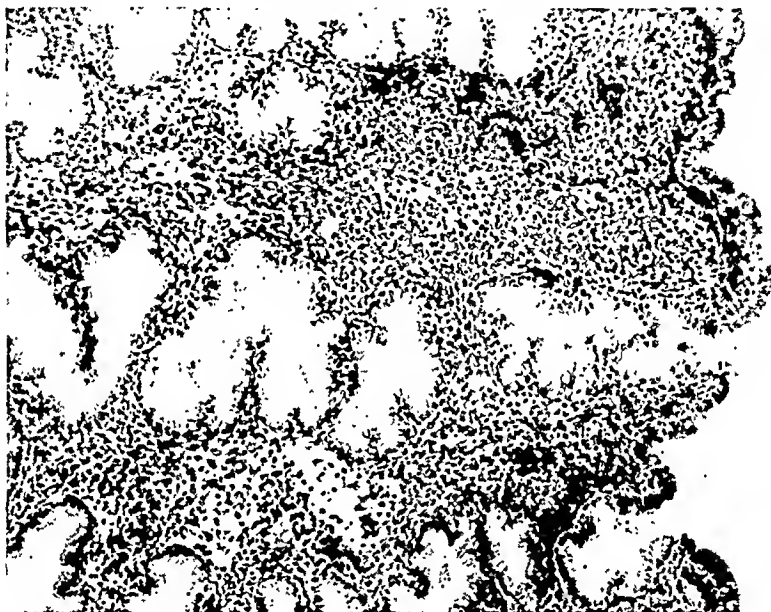


Fig. 2.—Late luteal phase produced with 120 mg. of estradiol and 1,200 mg. of pregnenolone.  $\times 160$ .

CASE 3.—P. Z.,\* aged 40 years, widow, was admitted to the Gynecological-Endocrine Clinic complaining of hot flushes every one-half to two hours, followed by attacks of excessive perspiration, joint pains over entire body, headache, and vertigo. Last menstrual period occurred eight months previously when a bilateral salpingo-oophorectomy for cystic ovaries was performed.

Bimanual examination revealed a small, atrophic, retrodisplaced uterus, measuring  $2\frac{1}{2}$  inches from external os to fundus. The vaginal mucosa was dry and pale. Cervix was atrophic and dilatable with extreme difficulty. Endometrial biopsy revealed atrophic remnants of an early follicular phase.

Dec. 24, 1939, to Jan. 4, 1940: Dimenformon, 4 mg. daily for twelve days.

Jan. 4, 1940, to Jan. 15, 1940: Dimenformon, 6 mg. plus 100 mg. pregnenolone daily for twelve days.

Jan. 18, 1940: A biopsy was taken and the diagnosis of the endometrial tissue was a late luteal phase (Fig. 3). At this time the uterus measured  $2\frac{1}{2}$  inches from external os to fundus.

January 18: There was spotty bleeding.

January 19 and 20: Patient reported bleeding which necessitated the use of five pads daily.

Flushes disappeared during medication and reappeared April 16, 1940.

\*See footnote page 87.

CASE 4.—C. L.,\* white, married, aged 28 years, was admitted to Gynecological-Endocrine Clinic complaining of hot flushes and nervousness, excessive perspiration, more marked during the night, and frequent frontal headaches. She had had a

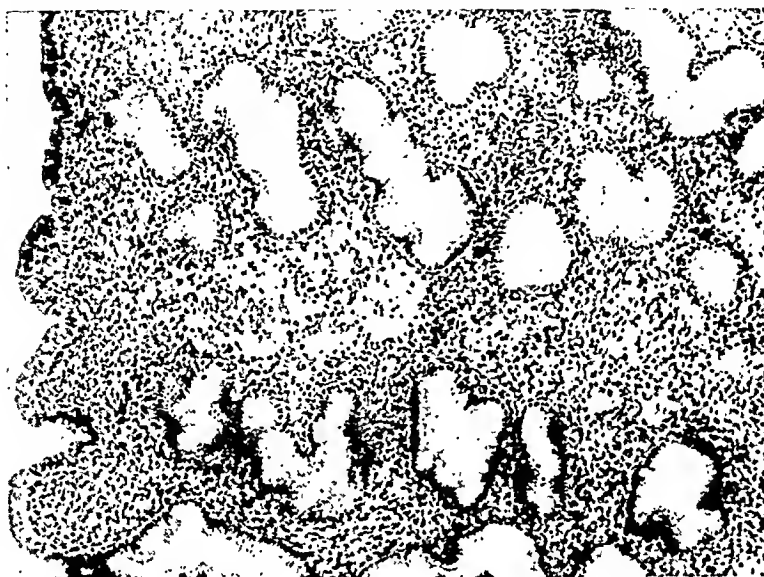


Fig. 3.—Mid to late luteal phase produced with 120 mg. of estradiol and 1,200 mg. of pregneninolone.  $\times 160$ .

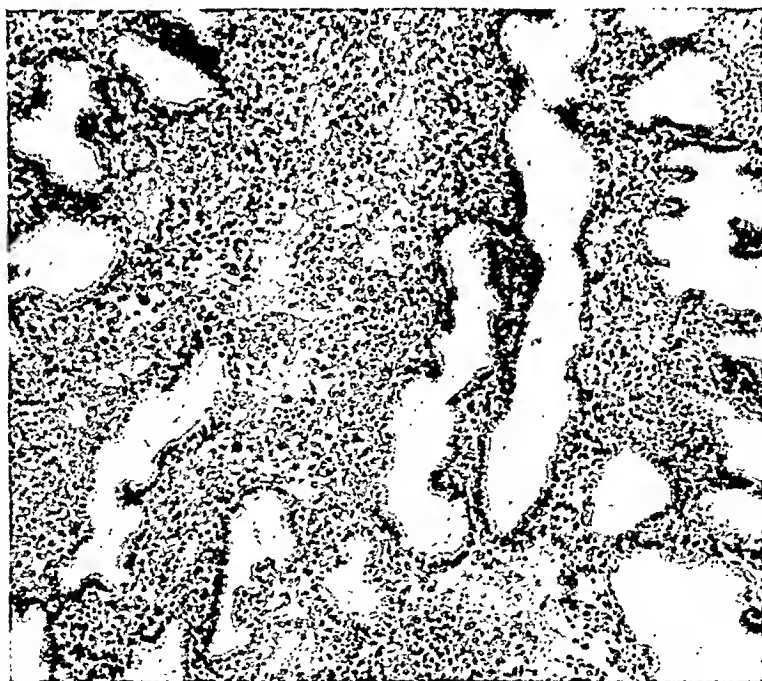


Fig. 4.—Mid to late luteal phase produced with 120 mg. of estradiol and 1,200 mg. of pregneninolone.  $\times 160$ .

bilateral salpingo-oophorectomy four years previously for bilateral dermoid cysts. Menstruation began at 13 years of age and was of four days' duration, with irregular intervals. She had had two normal pregnancies and one spontaneous miscarriage. There had been no menstruation since operation.

\*See footnote page 87.

Bimanual examination revealed the uterus to be slightly smaller than normal, in anterior position, freely movable, cervix small, well epithelized; uterus measured  $2\frac{1}{4}$  inches from external os to fundus. An endometrial biopsy specimen was diagnosed as atrophic endometrium.

Feb. 8 to 19, 1940 inclusive: Dimenformon 4 mg. daily for twelve days.

February 20 to March 2 inclusive: Dimenformon 6 mg. daily plus 100 mg. pregnenolone for twelve days.

March 5: An endometrial biopsy was taken and a moderate amount of tissue was recovered. Diagnosis was a mid- to late luteal phase of endometrium (Fig. 4). The uterus measured  $2\frac{1}{4}$  inches from external os to fundus. Patient menstruated March 6 to 9, normal flow. Headaches, backaches and flushes disappeared during medication. Flushes began to reappear two months later.

CASE 5.—M. S., aged 33 years, married, had had no menses for seven years, but had hot flushes one to three times during the day, constant fatigue, headaches, and dizziness; bilateral salpingo-oophorectomy, appendectomy 1925, one miscarriage, one stillbirth; for about four or five years following operation, menses occurred every three to four months for two or three days, moderate flow.

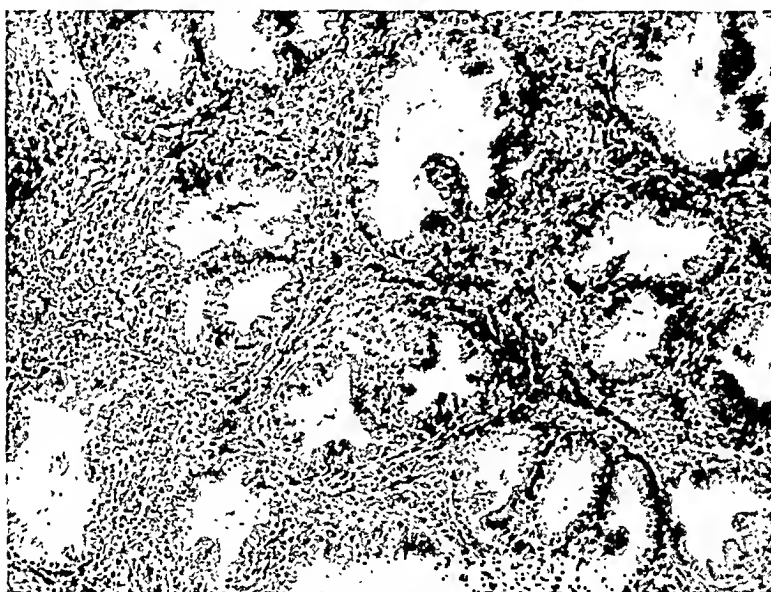


Fig. 5.—Late luteal phase produced with 120 mg. of estradiol and 1,200 mg. of pregnenolone.  $\times 160$ .

Bimanual examination showed the external genitals to be atrophic, vaginal orifice small, and barely admitting two fingers; cervix atrophic, well epithelized; uterus retroflexed and measured 2 inches from external os to fundus, dilatation rather difficult.

March 28, 1940: An endometrial biopsy was taken and scant endometrium obtained. The diagnosis was atrophic endometrium.

March 30 to Apr. 10, 1940: Dimenformon, 4 mg. daily for twelve days.

April 9 to 20: Dimenformon 6 mg. daily plus pregnenolone 100 mg. daily for twelve days.

April 23: Patient reported beginning of staining. An endometrial biopsy was taken and a moderate amount of tissue was obtained which was diagnosed as mid- to late luteal phase (Fig. 5). At this time the uterus measured  $2\frac{1}{2}$  inches from external os to fundus. There was bleeding from April 23 to 30, necessitating the use of two pads daily.

The flushes disappeared during medication and there was no difficulty with cervical dilatation after treatment. The patient was seen Aug. 6, 1940, at which time she had no return of hot flushes.

## COMMENT

The ultimate objective in the field of hormone therapy is replacement of the injectable endocrine products by oral medication. With this purpose in view, an attempt was made to produce, by means of oral medication in the human castrate, the actual changes occurring in the endometrium during a normal menstrual cycle. Many investigations have been made in the past with lower animals and primates, demonstrating the effectiveness of endocrine preparations. Yet it is well known that the differences between human and animal physiology prevent a common application of therapy. It is, therefore, desirable to utilize human physiology so far as possible, in order to ascertain definitely biologic potency.

Up to the present time the literature contains very few reports concerning pregnenolone, a new type of synthetic luteal hormone.

Inhoffen and Hohlweg<sup>3</sup> were able to produce a full-blown luteal phase in an infantile guinea pig uterus, previously stimulated with ethinyl estradiol, with 4 mg. of pregnenolone. Zondek and Rozin<sup>4</sup> report luteal endometrial changes in a previously estrinized secondary amenorrheics. In another instance bleeding similar to menstruation occurred several days after cessation of medication. Clauberg,<sup>5</sup> utilizing noncastrated amenorrheics, claims luteal changes following administration of 92 mg. of ethinyl estradiol plus 220 mg. of pregnenolone, 100 mg. of progynon C, and 300 mg. of pregnenolone, respectively. He never used more than 400 mg. of pregnenolone, and reports bleeding within six days of cessation of medication, yet none of his microphotographs really shows changes analogous to a normal twenty-two- to twenty-four-day endometrium. Salmon, Walter and Geiste have produced progestational changes in five postmenopausal women with 140, 480, 105, 500, and 540 mg. of pregnenolone, respectively, after intramuscular priming with amounts varying from 120,000 to 655,000 R. U. of estradiol benzoate. The second case showed a very good late luteal phase. There was no report of any bleeding after medication.

The dosage and timing of this investigation were based upon previously reported oral-parenteral experiments. In that series, 90 mg. of progestin parenterally over a twelve-day period produced endometrial changes comparable to a normal late luteal phase. In the present series, ten times that quantity was given orally to Case 1, 900 mg. in the form of pregnenolone, over a twelve-day period. An early to midluteal phase was produced; since this did not correspond to a late progestational phase, the dose in the other cases was stepped up to 13 times the amount. Cases 2, 3, 4, and 5 received therefore 1,200 mg. of pregnenolone over twelve-day periods and here the endometriums were of the late premenstrual type.

Bleeding which was described as menstruation occurred in all patients within forty-eight to seventy-two hours after cessation of medication. In addition, the usual premenstrual molimina were reported. Libido was increased in some and in others there was no change. Cases 2 and 5 showed some evidences of uterine growth. All degrees of atrophic changes disappeared with medication. Patients were completely free of the menopausal syndrome during medication and for some time afterwards.

As to a possible human unit, or the amounts of both hormones which are actually necessary to produce the desired endometrial changes, assuming that the ratio of effectiveness between oral and parenteral administration is 1:13; then in actual crystalline substance 9 mg. of estradiol and 90 mg. of progesterone are approximately the amounts utilized in normal menstrual cycles. Some investigators believe that the ratio varies from 1 to 6:8. This may be true if biologically active extracts were employed; however, the above findings are based entirely upon the use of synthetic preparations.

The value of this research problem offers future possibilities in the treatment of certain endocrine disturbances. In instances of atrophic uteri due to intrinsic changes, present-day methods of pituitary and ovarian stimulation, which are very questionable, are insufficient to re-establish normal menstrual cycles. The uterus must be in a state receptive to normal ovarian secretion. In many instances of secondary amenorrhea, usually preceded by months of hypomenorrhea, this does not exist, in spite of the presence of a normal pituitary-ovarian relationship. In this type of endocrine derangement, oral therapy of this kind should prove of value. At the present time oral therapy is beset with several difficulties, namely the necessity of high dosage and the consequent expense. With improved chemical methods, this expenditure may eventually be lowered, for small doses orally are of no value in severe endocrine dyscrasias.

#### SUMMARY

Six female castrates were treated with synthetic oral estradiol and progestin. The total amount used was 120 mg. of estradiol and 900 to 1,200 mg. of pregnenolone. Progestational changes were produced in all cases. In four instances, the endometrium approximated that of a late luteal phase, whereas one with smaller dosage showed only an early luteal change. The symptoms and atrophic changes characteristic of the menopause completely disappeared during medication and returned months afterward in all patients with one exception. Uterine growth was manifest in two instances. Bleeding occurred in all patients within forty-eight to seventy-two hours after cessation of medication. The ratio of effectiveness between oral and parenteral administration is approximately 1:13.

I wish to express my grateful appreciation to Dr. Walter T. Dannreuther for his kind assistance and constructive criticisms, and to Miss Mary Chin for the preparation of the sections.

#### REFERENCES

- (1) *Neustaedter, T.*: AM. J. OBST. & GYNEC. 29: 680, 1935. (2) *Idem*: Ibid. 38: 609, 1939. (3) *Inhoffen, H. H., and Hohlweg, W.*: Naturwissenschaften 26: 96, 1938. (4) *Zondek, B., and Rozin, S.*: Lancet 1: 504, 1939. (5) *Clauberg, C.*: Zentralbl. f. Gynäk. 62: 1745, 1939. (6) *Salmon, U. J., Walter, R. I., and Geist, S. H.*: Proc. Soc. Exper. Biol. & Med. 40: 252, 1939.

## ESTRIN POTENCY AND BASAL METABOLISM\*

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EXPERIMENTS reported previously (Collett, Smith, and Wertenberger, 1937) have shown that estrin administration affects the basal metabolic rate appreciably. We have since tried to see whether the potency of the various estrins, given orally or by injection, could be assayed by their effect upon the basal metabolic rate.

Our subjects were five women, 30 to 42 years of age, who had been subjected to panhysterectomy. They were first studied three to nine months after operation. By means of daily metabolism tests, we established the reaction of each patient to varying doses of estrin given in the same form and by the same route, and then proceeded to a comparison of oral and injected doses of estrone or of oral doses of estrone and of estriol. The estrins used were: Estrone (oil theelin† and Ovex Leo tablets‡) and estriol theelol capsules.§

Except with Cases M and N, medication was continued daily for a week. Metabolism tests were made daily or on alternate days. Instead of indicating every metabolism test as heretofore, we show in the graphs only the average basal metabolic rate for each week; before, during, and after medication. The vertical lines in Charts 1 and 2 indicate the range of variation in each week. Basal metabolic rate is stated in percentage of the premedication level, which is always somewhat below the Harris-Benedict standard in these subjects.

The unequal effect of large and small doses given by the same route appears in all the graphs. The average basal metabolic rate of Patient K (Fig. 1) was raised 10 per cent by six daily doses of 500 I.U. oil theelin given by injection. A higher dosage (1000 I.U.) produced a smaller rise, 5 per cent. A similar difference in metabolic response to unequal dosage was observed in this patient on orally administered oil theelin: a rise of 9 per cent on 1000 I.U. and of 5 per cent on 2000 I.U. Patient L (Fig. 2) showed a rise in basal metabolic rate of 15 per cent on 500 I.U. injected oil theelin, but a smaller immediate rise (5 per cent) followed by a delayed rise of 10 per cent on 1000 I.U. doses. Patients M and N (Fig. 3) were given larger doses of injected oil theelin: one dose of 10,000 I.U. or 5 doses of 2,000 I.U. Patient M's basal metabolic rate fell 2 per cent in the week of the broken dose and 5 per cent in the week of the single large dose. Patient N's basal metabolic rate was unchanged in the week of medication, but in the second and third weeks showed a greater rise with the broken dose than with the single large dose. Patient O (Fig. 4), when given estrone (Ovex) orally, showed a drop in basal metabolic rate of 2 per cent on 1,000 I.U. and of 5 per cent on 2,000 I.U. Although the amount and direction of the change in basal metabolic rate varied with

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§Parke, Davis & Co.

the individual, it is clear in every case that larger doses differed from smaller doses in causing a smaller rise or a greater fall in basal metabolic rate. We have, therefore, used this method for estimating the relative potency of estrone and estriol given orally, and of injected versus orally administered estrone.

### CASE K

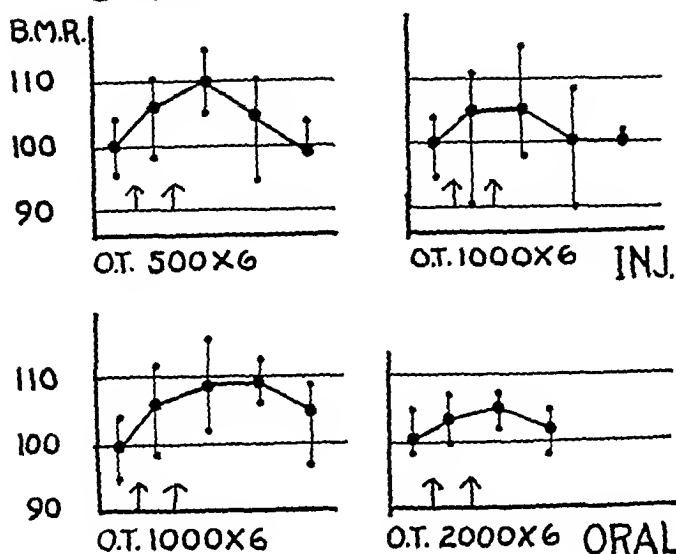


Fig. 1.

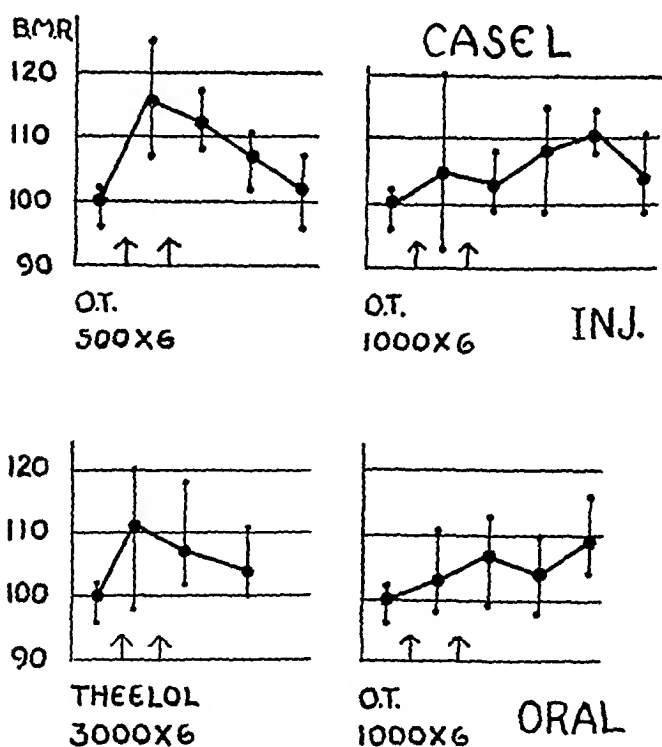


Fig. 2.

With Patient K, 1,000 I.U. injected estrone (oil theelin) produced a smaller rise than 1,000 I.U. taken orally, but a slightly greater rise than 2,000 I.U. taken orally. The potency of injected estrone was therefore almost double that of oral

estrone. With Patient L a comparison of basal metabolic rate averages indicates that 1,000 I.U. injected estrone (oil theelin) was slightly more potent than 2,000 I.U. of estrone (Ovex) taken orally. With Patient O, 1,000 I.U. injected estrone (oil theelin) gave a fall in basal metabolic rate of 5 per cent with a much delayed rise, while 2,000 I.U. estrone (Ovex) given orally caused an almost equal fall followed by a prompt rise of 10 per cent, indicating that estrone was a little more than twice as potent when injected than when given orally. Thus with all 3 patients, injected estrone seemed 1 to  $2\frac{1}{2}$  times as potent as the same dose taken orally.

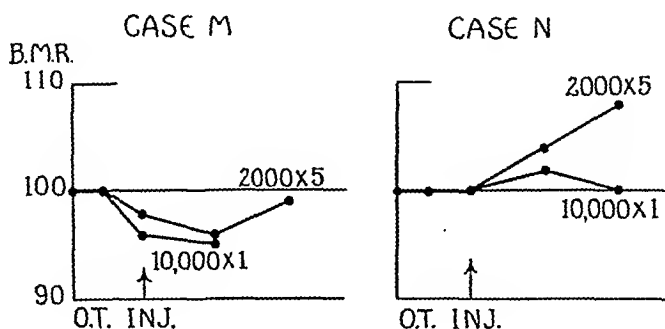


Fig. 3.

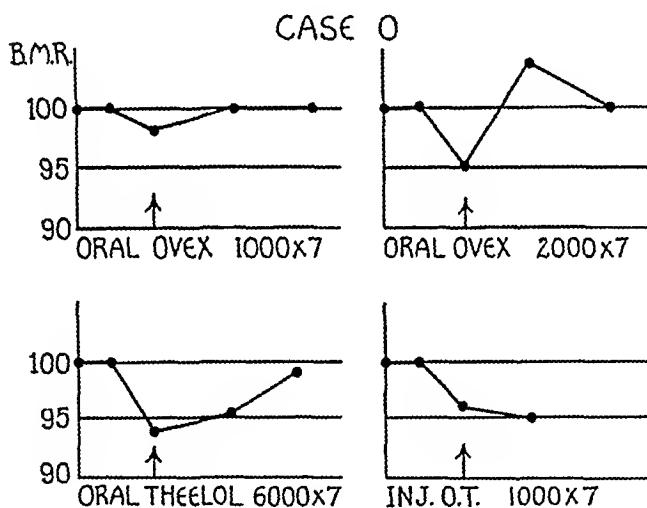


Fig. 4.

Orally administered estriol was compared with oral estrone in two patients. With Patient L, 3,000 I.U. (0.18 mg.) of estriol (theelol) led to an immediate rise of 10 per cent, slightly less than that induced by 500 I.U. injected estrone; while 1,000 I.U. oral estrone (oil theelin) led to a slower rise of 3 to 10 per cent. With this patient 1,000 I.U. oral estrone was, therefore, more potent than 3,000 I.U. oral estriol. With Patient O, 2,000 I.U. doses of oral estrone (Ovex) led to an immediate fall in basal metabolic rate of 5 per cent, followed in the next week by a rise of 10 per cent; while oral estriol (theelol) in 6,000 I.U. doses led to the same immediate drop and a slower rise. With Patient O, therefore, 6,000 I.U. of oral estriol seemed slightly more potent than 2,000 I.U. of oral estrone. In both patients, then, oral estriol appeared to be about one-half as effective as oral estrone, and about one-sixth as effective as injected estrone, unit for unit.

Daily reports on symptoms were made by all the patients, and these, in general, support the estimates of potency based upon basal metabolic rate fluctuations, although small differences are less definitely indicated. We have found that the patient's sense of energy is a clearer index of potency than the lessening of her hot



flushes. Patient K's reports indicated a slightly greater potency for injected than for oral estrone. Patient O's reports showed injected estrone about twice as potent as oral estrone and four to five times as potent as oral estriol. Patient L's reports (Fig. 5) showed injected estrone twice as potent as oral estrone and three to four times as potent as oral estriol. It was difficult to get accurate reports from the patients, and the difficulty was increased by the fact that medication was not continuous and was generally barely enough to diminish symptoms without abolishing them. When dosage is close to the optimal level for a given patient (as with Patients M and N), the subject is likely to report feeling better on consecutive small doses than on a large single dose, probably because a larger dose, unless continuous, upsets her endocrine balance.

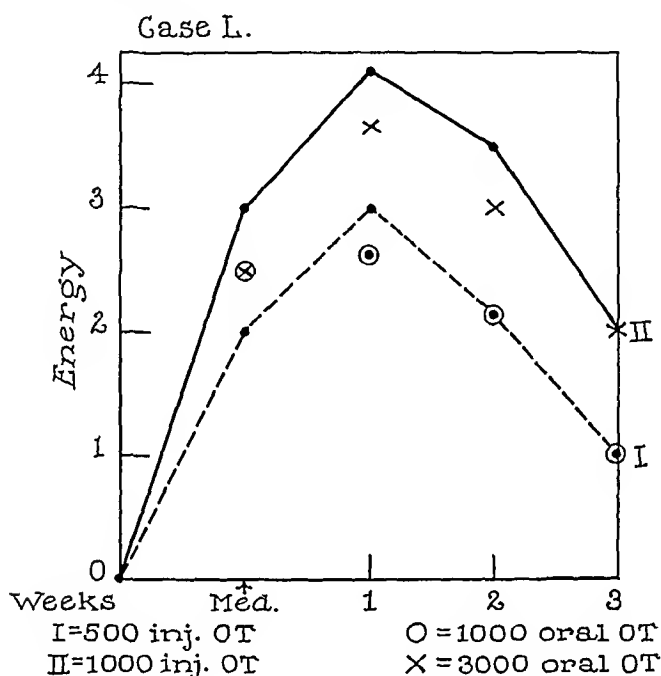


Fig. 5.

A more satisfactory estimate of potency based upon personal reports was obtained from a patient outside this series, who received continuous daily medication instead of medication for a single week. She was a woman of 30 whose ovaries were intact but functioning poorly. A record covering 3 consecutive menstrual cycles showed the results as shown in Table I.

TABLE I. CYCLE DAYS

CYCLE	DAYS		DAILY DOSAGE IN I.U. ORALLY	
	BAD	GOOD	OVEX	THEEOL
1	70	32	----	1000
2	57	43	----	1800
3	45	55	1800	----

Too low a dosage (1,000 I.U. theelol) gave a large proportion of days of extreme fatigue and nervousness. A larger dosage of theelol (1,800 F.V.) improved the record, and 1,800 I.U. of ovex (estrone) improved it still more. This result agrees with the estimate of the relative potency of these two estrins based upon basal metabolic rate fluctuation observed in our other patients.

It is worth noting that our records show all the effects of estrin upon basal metabolism reported by other authors: increase, decrease, and

no effect. It is now clear that this apparent chaos can be explained by the size of the dose in relation to the endocrine balance. It seems probable that the action of estrin upon basal metabolism is first through the thyroid directly and then indirectly by way of the anterior pituitary (Victor and Anderson).

A halving of potency by the oral route, such as we have observed with estrone, is found with many drugs, and agrees with the ratio observed by Mazer and Israel.

Our finding that oral estriol is less potent than oral or injected estrone disagrees with Rowe and Simond but agrees with Mazer and Israel, Nelson and Overholser, and D'Amour and D'Amour. D'Amour and D'Amour suggest that part of the difficulty may lie in the manufacturer's use of different methods of assay for the two substances.

#### SUMMARY

Relatively small doses of estrin produce a larger rise or a smaller fall in basal metabolism than do heavier doses given to the same individual. Differences in the potency of different estrins given by the same or different routes can, therefore, be estimated by means of the basal metabolic rate. On this basis, oral estriol appears to be less potent, unit for unit, than oral estrone; and oral estrone only slightly less potent than injected estrone.

We are greatly indebted to Professor Sollmann for advice on this work; to Dr. Joseph T. Smith and Dr. Robert Faulkner for referring patients from the Department of Gynecology at Lakeside Hospital; and to the Council on Pharmacy of the American Medical Association for a grant in aid.

#### REFERENCES

- Collett, Mary E., Smith, Joseph T., and Wertenberger, Grace E.: *AM. J. OBST. & GYNEC.* 34: 639, 1937. D'Amour, Fred E., and D'Amour, Marie C.: *Endocrinology* 22: 583, 1938. Mazer, Charles, and Israel, S. Leon: *J. A. M. A.* 108: 163, 1937. Nelson, Warren O., and Overholser, Milton D.: *Endocrinology* 20: 473, 1936. Rowe, L. W., and Simond, A. E.: *J. Am. Pharm. A.* 25: 201, 1937. Victor, Joseph, and Anderson, Dorothy H.: *Am. J. Physiol.* 122: 296, 1938.

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Takata, M., Suzue, K., and Nisi, H.: *The Relation of Physical Constitution to Uterine Tumors Studied by Pelvic Measurements*, *Jap. J. Obst. & Gynec.* 22: 265, 1939.

From a study of a large number of women with fibroids, ovarian cysts and carcinoma of the uterus, the authors conclude that uterine cancer occurs in short, heavy women, whereas fibroids of the uterus and ovarian cysts are found in thin individuals.

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blind. He has also found a very high incidence of defects of the palate in fetuses from his low vitamin A mothers. Warkany<sup>10, 11</sup> has shown that rats born of animals on a grossly deficient diet usually had deformities of the long bones, sternum, or mandible. It seems not impossible that diets grossly defective in certain of the essential amino acids may in part be responsible for the defective embryonic development of certain fetal tissues. Murphy and Bowes<sup>12</sup> have investigated this possibility but without definite conclusions.

The intrauterine sensitization of the fetus to food allergens does occur, according to Ratner<sup>13</sup> and his co-workers who have produced a good deal of evidence of this phenomenon. It seems not unlikely that many of the eczemas, asthmas, and allergic gastrointestinal reactions of early infancy are the result of intrauterine sensitization. Ratner believes that such intrauterine sensitization tends to occur from the excessive use of certain foods by expectant mothers who have allergic tendencies.

It is possible also that the physical stamina or constitutional adequacy of a newborn infant may depend to some degree upon the adequacy of its mother's diet and her body stores of certain of the vitamins and amino acids. Roentgen examination of a group of newborn infants has shown that the severity of round bone sears resulting from the birth process is very much greater in those children born of mothers whose diet was *grossly* defective in the muscle- and gland-building elements and in vitamins. This fact suggests that children from inadequately nourished mothers may suffer a greater neonatal growth interruption than will those of well-nourished mothers.<sup>14, 15</sup>

#### TOXINS AND DRUGS

Mosher<sup>16</sup> has found that mapharsen, quinine, or sodium salicylate when fed or injected into pregnant animals, produces hemorrhages in the labyrinth of the fetuses without producing similar hemorrhages in the mother. Mapharsen produced the greatest hemorrhages which were located in the scala vestibuli, vestibule, and semicircular canals. Taylor<sup>17</sup> has reported an increased incidence of congenital deafness among the offspring of mothers who, during the malaria season, were heavy users of quinine. He attributes this high incidence of deafness to the effects of quinine upon the fetal inner ear. Mosher's work lends some credence to these observations, although doses used far exceeded those which normally are used therapeutically in human beings. Adair and Stieglitz,<sup>18</sup> however, have observed no harmful effects from quinine. Burnett<sup>19</sup> and Petzey<sup>20</sup> have reported morphinism in the infants of mothers who were habitual morphine users.

#### THE ENDOCRINE GLANDS

The interrelationship of the maternal and fetal endocrine systems constitutes an interesting subject for study. It is generally accepted that the fetal and maternal endocrine systems function to some degree at least in a complementary fashion. The work and writings of Rupp,<sup>21</sup> Soule,<sup>22</sup> Hamblen,<sup>23</sup> Schlossman,<sup>24</sup> and many others have amply demonstrated that the two endocrine systems complement each other. This complementary relationship is well demonstrated when pregnancy is

assures that many minimal stimuli of this sort are lost to the fetus. These protective mechanisms reduce the range of environmental differences and eliminate many of them. That many such changes and differences do remain, however, is undeniable, and I shall discuss some of these and their significance in the following pages.

#### NUTRITION

Attempted reduction in weight of the fetus by restricting maternal diet, in order to facilitate ease of delivery, is a procedure which still enjoys some popularity in certain sections of the country. This procedure has enjoyed little or no success because the fetus acts as a parasite and, if necessary, satisfies its nutritional needs at the expense of the mother's body.

According to Adair<sup>1</sup> and others, the growth of the fetus seems to be independent of fats and carbohydrates in the maternal diet, as long as the diet is not grossly deficient in total calories. Restrictions of diet are effective in controlling fetal weight only when so drastic as to reduce materially the mean levels of maternal blood sugar, amino acids, and perhaps fatty acids, a situation met with only in partial starvation. Jonen<sup>2</sup> and others have been able to produce animal fetuses of abnormally low birth weight through actual starvation of the mother with marked depletion of her tissues during pregnancy. In case of starvation even those mechanisms for the maintenance of normal amino acid and sugar levels in the blood fail, and, since the whole diffusion mechanism is dependent upon relative levels in the maternal and fetal circulations, the amount of nutritive materials transmitted through the placental membrane is decreased. In diabetes where the mechanism for maintaining a normal basal blood sugar level is incapable of functioning, there is a deposition of additional quantities of fetal fat, although here there is some question as to an aberrant function of the pituitary gland contributing to the production of the excessive weight.

Maxwell<sup>3</sup> has shown that in starvation maternal mineral reserves may be so depleted as to produce a condition of fetal rickets. Wolfe<sup>4</sup> reports that the teeth of such infants are also defective. Adair<sup>1</sup> and Geller<sup>5</sup> says that vitamin deficiencies in the mother's diet may seriously injure the fetus. Rector<sup>6</sup> and others have shown that a vitamin D deficiency during pregnancy predisposes the child to early rickets. I have recently had occasion to examine the skeletal x-rays of a large group of breast-fed infants taken at one month of age, whose mothers, living in the slums of a large city, suffered from rather severe malnutrition during pregnancy particularly as regards vitamin D and milk. The incidence of active and well-developed rickets in this breast-fed group at the age of one month was very high. Guggisberg,<sup>7</sup> on the other hand, has demonstrated that young rats whose mothers received large doses of irradiated ergosterol during the period of gestation were extremely resistant to rickets. Sontag and Munson<sup>8</sup> have demonstrated that vitamin D fed in moderately excessive amounts will produce overly mineralized bones in the fetus, and extremely excessive amounts will produce demineralization. Scurvy tends to appear earlier and in a much more malignant form in infants whose mothers' diets were grossly deficient in vitamin C. Hale<sup>9</sup> has stated that pig fetuses born of mothers fed a diet grossly deficient in vitamin A are born with defective eyes and are permanently

I have observed a few cases of hypothyroidism during pregnancy in which the newborn infant had a somewhat retarded skeletal development and was inactive, lethargic, and retarded in its behavior pattern. Within a few weeks after birth a sharp spurt in the development of ossification centers occurred together with rapid growth in length and a marked change in the behavior pattern, toward more activity and alertness. One interpretation of these cases is that these infants during their intrauterine lives had been producing thyroxin at a very rapid rate but since each had had to supply not only its own thyroxin needs but part of those of a "poor relative," it had not been able to do both jobs adequately. However, when birth destroyed the maternal-fetal relationship, each fetus was producing an excess of thyroxin over its normal neonatal needs and during the course of a very few weeks the effects of this more than ample thyroid secretion rapidly became apparent in the growth spurt and behavior changes already described. Such material is obviously inadequate to justify any conclusion. This growth spurt appeared to level off during the course of a year, suggesting an adjustment of thyroid function to a level of infant needs. Whether this adjustment always occurs or whether in some instances in children who have an inadequate iodine intake the thyroid sometimes undergoes degeneration with resulting cretinism, as has been suggested by Patterson,<sup>36</sup> is a subject for further investigation.

Experimental work on the effects of excessive amounts of the thyrotropic element of the pituitary in the mother's blood upon fetal thyroid has been reported (Grumbrecht and Loeser<sup>37</sup>), of the gonadotropic hormone on the fetal ovary<sup>38</sup> and of the suprarenal gland upon the fetal ovary (Tanioka<sup>39</sup>). The work is not conclusive and is inadequate to justify an assumption that maternal hyperthyroidism could be expected to cause changes in the development and function of the fetal thyroid. That such maternal thyroid overfunction may produce a depressing effect upon the developing fetal thyroid is, however, a distinct possibility.

#### OTHER FACTORS

Hooker<sup>40</sup> has shown that the human fetus is capable of responding to tactile stimuli eight and one-half weeks after the fertilization of the egg. Peiper<sup>41</sup> in 1925 reported instances of sound perception and movement responses by the human fetus, as did Ray.<sup>42</sup> Spelt,<sup>43</sup> in 1938, reported the successful conditioning of the human fetus to sound stimuli. My colleagues and I have for several years been investigating the factors influencing fetal activity level and producing an activity response. Deeply disturbed maternal emotion produces a marked increase in activity of the fetus probably as a result of increased adrenalin level in the maternal and, therefore, the fetal blood. Severe maternal fatigue increases fetal activity probably through changes in maternal and, therefore, fetal blood chemistry. The startle reflex is active and a sound of proper pitch, intensity, and proximity will produce an instantaneous and convulsive movement probably through auditory nerve stimulation by bone conduction. These findings have all been mentioned in pre-

complicated by diabetes. Heilberg<sup>25</sup> found a marked increase in the number of islands of Langerhans in the fetal pancreas when mothers were diabetics. Gray and Feemster<sup>26</sup> found the insulin content of the pancreas of fetuses of diabetic mothers twenty-four times as high as that in the mother's pancreas. Weiner<sup>27</sup> found that the pancreas of infants of diabetic mothers contained much more insulin than did those of infants of nondiabetic mothers. Gordon<sup>28</sup> and others have reported an improvement in diabetic mothers during pregnancy presumably due to the passage of fetal insulin into the maternal circulation. In such cases the newborn infants usually developed a marked hypoglycemia as a result of the compensatory hyperfunction of its pancreas.

Teel,<sup>29</sup> Hain,<sup>30</sup> Sontag and Munson,<sup>31</sup> Watts,<sup>32</sup> and others have shown that by the introduction of large doses of Evans' growth hormone to pregnant rats during the last two weeks of the period of gestation it is possible to produce rat fetuses which are larger than control animals. Hamilton and Wolfe<sup>33</sup> report that they injected testosterone propionate into pregnant animals with the result that females in the litters from these animals showed retardation of sexual development. Arnold<sup>34</sup> claims to have been able to influence the weight of the human fetus by the administration of thyroid to mothers during their last months of pregnancy. Patterson, Hunt, and Nicodemus,<sup>35</sup> and others have demonstrated that in patients with low thyroid function the secretion of the fetal thyroid gland supplements to some degree the production from the maternal thyroid. These and many other examples indicate that fetal and maternal endocrine glands act as complementary production units. Such a complementary endocrine relationship immediately stimulates speculation as to what may be the effects both neonatally and later upon the thyroid function of human infants born of mothers with thyroid deficiency or hyperfunction during pregnancy. Might not maternal hypothyroidism throw an excessive load upon fetal thyroid with a resulting hyperplasia, hypertrophy, and an over-functioning thyroid at birth? Conversely, might maternal hyperthyroidism depress fetal thyroid function? Patterson, Hunt, and Nicodemus<sup>35</sup> have reported that the first of these phenomena does occur, that children of hypothyroid mothers have hyperplastic thyroid glands at birth. As already stated, infants with over-functioning islands of Langerhans as a result of maternal diabetes exhibit a marked hypoglycemia within a few hours after birth. A gradual adjustment of insulin production then takes place. What happens to the endocrine economy of children with hyperfunctioning thyroids as a result of maternal hypothyroidism and what is their developmental history? Patterson and others<sup>35</sup> believe that some congenital goiters are the result of fetal thyroid hyperplasia from maternal absorption of fetal thyroxin production. They believe that these thyroids which are hyperactive at birth undergo an involution within a few months and usually function normally thereafter. The evidence on this subject is as yet inadequate to justify any positive statement as to what effect upon the thyroid economy of a child hypo- or hyperthyroidism of its mother during the gestation period will have. The amount of nonthyroxin iodine in the mother's blood, the severity of the mother's thyroid abnormality, and perhaps other factors may in many instances alter the picture greatly. That such a maternal thyroid disturbance does affect fetal thyroid development and function and may be a very important factor in establishing the level of post-natal thyroid function seems probable.

turbances of the mother during the later months of pregnancy seem to be important. Any such effect must, of course, depend for its mechanism upon changes in the chemistry of the mother's and therefore the fetus's blood as a result of these emotional changes since it is only in such a manner that central nervous system stimulation in the mother could affect the fetus. Acetylcholine and adrenalin are two substances either or both of which may well be involved. Preliminary experiments suggest the importance of acetylcholine. Whatever the chemical change responsible, the autonomic nervous systems of infants born of mothers under such conditions frequently show several evidences of autonomic instability. In addition to regurgitation, diarrhea, or constipation, they may show greater than average heart rate ranges, vasomotor instability or changes in respiratory pattern. Those cases in which a major disturbing factor was known to have occurred and been present for a considerable period of time during later months of pregnancy were recently selected from our group. In one instance, the husband of the woman became insane midway in the pregnancy but continued to live with the wife, although frequently violent and never entirely rational. In another, the mother was an unmarried woman of thirty-five who had suddenly learned that the father of her child, to whom she had expected to be married, was already a married man. To add to her distress her very severe family made life entirely miserable for her. In the eight cases where emotional distress was most obvious and existed over a long period of time, seven infants had moderate or severe feeding difficulties in the form of inability to retain food. In some of these cases there was a tendency to frequent stools for several months. Such observations stimulate speculation but are, of course, inadequate to substantiate the explanation offered here of the origin of some of the early feeding difficulties encountered. The possibilities are intriguing, however, and seem to justify further study.

#### SUMMARY AND CONCLUSIONS

The evidence available in the literature from both animal experimentation and the observation of pregnant women and the children they bear are indications that differences in environment during the fetal period may be of great importance in the development of the child both before and after birth. Such factors as the drugs women use during pregnancy, their nutrition, endocrine status, emotional life and activity level during gestation may contribute to the shaping of physical status, behavior patterns, and postnatal progress of the children they bear.

#### REFERENCES

- (1) *Adair, F. L.*: J. A. M. A. 99: 433, 1932. (2) *Jonen, P.*: Ztschr. f. Geburtsh. u. Gynäk. 103: 192, 1932; Zentralbl. f. Gynäk. 52: 2999, 1928. (3) *Maxwell, J. P., Hu, C. H., and Turnbull, H. M.*: J. Path. & Bact. 35: 419, 1932. (4) *Wolfe, J. J.*: Am. J. Dis. Child. 49: 905, 1935. (5) *Geller, F. C.*: Monatschr. f. Geburtsh. u. Gynäk. 93: 350, 1933. (6) *Rector, J. M.*: J. Pediat. 6: 161, 1935. (7) *Guggisberg, H.*: Arch. f. Gynäk. 137: 710, 1929. (8) *Sontag, L. W., Munson, P., and Huff, E.*: Am. J. Dis. Child. 51: 302, 1936. (9) *Hale, F.*: Am. J. Ophth. 18: 1087, 1935. (10) *Warkany, J., and Nelson, Rose C.*: Science 92: 383, 1940. (11) *Warkany, J., and Nelson, Rose C.*: Anat. Rec. 79: 83, 1941. (12) *Murphy,*

vious reports (Sontag and Wallace;<sup>44</sup> Sontag and Richards<sup>45</sup>). The significance of these various stimulating factors in terms of the physiologic, anatomic, and behavior patterns of the newborn infant is less well understood than are their immediate effects. Such stimuli must be very common. My associates and I have had mothers complain of marked fetal activity from the vibration of a washing machine and from piano concerts. Reports of increased fetal activity to the degree of maternal discomfort are not uncommon during violent emotional upsets. We have found activity levels differing as much as 1000 per cent in various fetuses over the last three months of pregnancy.

For a number of years we have been studying the differences in physical and behavior characteristics of fetuses at birth in relationship to their activity prenatally and have made the following observations.

1. The fetuses which had been very active during the last two months of their intrauterine life from maternal emotional distress, fatigue, or other causes, tend to be light in weight in relationship to their length, and show a minimum amount of fat storage. It seems probable that sugar which in an inactive fetus would be converted and stored as fetal fat is burned for energy production in the active fetus (Sontag<sup>46</sup>). The diffusion mechanism of the placenta is such that a completely compensatory increase for an unusual demand for sugar does not occur because of the fetus's mechanism for maintaining basal blood sugar level. Increased transmission of sugar through the placenta is dependent upon an increased disparity between maternal and infant blood sugar levels.

2. There is some evidence, not yet conclusive, that the motor development of fetuses which have been active during the latter half of pregnancy is more advanced during the first year than is that of inactive fetuses (Richards and Newbery<sup>47</sup>). The differences are measured by means of responses to the Gesell schedule at six and twelve months. One possible explanation of this finding is that the increased use of the nervous system during the period of myelination facilitates the development of the nervous system. Animal experimentation suggests that the myelination of specific nerves can be accelerated by stimulation of the nerves, and there is, of course, considerable relationship between the function of a nerve fiber and its state of myelination.

I have, I believe, observed a relationship between some of the early feeding difficulties of infants and prenatal stimulation. In these instances disturbances of gastrointestinal motility, tone and function, manifested by excessive regurgitation, dyspepsia, and perhaps by diarrhea, may have resulted from the development prenatally of an irritable and hyperactive autonomic nervous system. Irritable or poorly balanced adrenergic-cholinergic systems probably constitute an important part of the rather poorly defined syndrome commonly labeled constitutional inadequacy or nutritional diaphysis. Early feeding difficulties based upon motor and secretory abnormalities of the gastrointestinal system are in many instances of autonomic origin. The presence of feeding difficulties of a motor or secretory nature from birth must presume their etiology and basic disturbances during intrauterine life. In prenatal development of such a condition, prolonged nervous and emotional dis-



In the hope of improving the results, our routine of treatment has been altered considerably during the last five years. In 1936, radium was administered in massive doses, 8,400 mg. hr. within the uterine cavity and on the vaginal aspect of the cervix. The application was made either with a gold T-tube or with a Swedish box per vaginam and platinum tubes intrauterine. This was supplemented by fractionated high voltage therapy at 200 k.v. to 1,400 r. on 4, 6, and 8 ports and 900 to 1,200 r. on a perineal port. Many times a second high voltage series was given in from three to six months.

In 1937, we began to fractionate the radium treatment after the manner of Regaud and the high voltage treatments were routinely given before the radium was applied.

#### METHOD

Early in 1938 new apparatus inaugurated high voltage treatment at 400 k.v. thus permitting more efficient depth dosage in heavier women. The routine became 2,400 r. on each of four ports and 900 r. on the perineum. High voltage treatment was repeated in a number of patients. Radium followed the primary high voltage series in the Regaud method. This routine was continued throughout the greater part of 1939, and the results of treatment were the best in the records of the Institute.

Late in 1939, a vaginal cone was adopted instead of the perineal port to supplement the pelvic high voltage cross-fire. By this means, a dose of 3,000 r. was delivered directly on the cervical area. A central posterior field was added or, in very heavy women, two lateral fields. Physical charts showed that the depth dose had a very satisfactory concentration and distribution. The immediate effect was impressive in the rapidity with which advanced lesions responded, but as will be seen complications have arisen and a revision of the method is indicated.

There has been much speculation as to the cause of the variation in response to irradiation. In tumors, the importance of cell type and degree of cell dedifferentiation have been emphasized. We have never been impressed by this theory. The same variation appears in the mal effect of irradiation on the normal tissues of different individuals. Is it not possible that radiosensitivity is personal rather than inherent in the tumor cell? In this present study, comparable patients received approximately the same irradiation and in some the results were satisfactory while in others the damage to normal tissue was irreparable.

Radiation sickness, cystitis, and proctitis are all fairly frequent developments during or immediately following treatment. Occasionally, they have interfered with the course of therapy. Nausea usually responds to a combination of nembutal, liver extract, and vitamin B. Cystitis is much less frequent when a self-retaining catheter keeps the bladder empty during radium treatment and the careful placing and packing off of vaginal applicators and the avoidance of central high voltage ports will prevent unnecessary injury to bladder or rectum.

Fever and infection during the course of treatment have caused much concern. Routine cultures are taken from the cervix because of the

- D. P., and Bowes, A. D.*: AM. J. OBST. & GYNEC. 37: 460, 1939. (13) *Ratner, B., and Greenburgh, J. E.*: J. Allergy 3: 149, 1932. (14) *Sontag, L. W.*: Am. J. Dis. Child. 55: 1248, 1938. (15) *Sontag, L. W., and Harris, L. M.*: Am. J. Dis. Child. 56: 1248, 1938. (16) *Mosher, H. P.*: Laryngoscope 48: 361, 1938. (17) *Taylor, H. M.*: Arch. Otolaryng. 20: 790, 1934. (18) *Adair, F. L., and Stieglitz, E. J.*: Obstetric Medicine, Philadelphia, 1934, Lea & Febiger, p. 227. (19) *Burnett, S. C.*: Med. Herald 39: 161, 1920. (20) *Pettey, G. E.*: South. M. J. 5: 25, 1912. (21) *Rupp, H.*: Arch. f. Gynäk. 143: 80, 1930. (22) *Soule, S. D.*: AM. J. OBST. & GYNEC. 35: 309, 1938. (23) *Hamblen, E. C.*: Endocrine Gynecology, Baltimore, 1939, Charles C Thomas, p. 66. (24) *Schlossman, H.*: J. Physiol. 92: 219, 1938. (25) *Heilberg, K. A.*: Virchows Arch. 287: 629, 1932-1933. (26) *Gray, S. H., and Feemster, L. C.*: Arch. Path. & Lab. Med. 1: 348, 1926. (27) *Weiner, H. J.*: AM. J. OBST. & GYNEC. 7: 710, 1924. (28) *Gordon, W. H.*: Ohio State M. J. 32: 540, 1936. (29) *Teel, H. M.*: Am. J. Physiol. 79: 170, 1926. (30) *Hain, A. M.*: Quart. J. Exper. Physiol. 22: 71, 1932. (31) *Sontag, L. W., and Munson, P.*: Am. J. Physiol. 45: 517, 1933. (32) *Watts, R.*: AM. J. OBST. & GYNEC. 30: 174, 1935. (33) *Hamilton, J. B., and Wolfe, J. M.*: Anat. Record 70: 433, 1938. (34) *Arnold, L. E.*: AM. J. OBST. & GYNEC. 39: 99, 1940. (35) *Patterson, W. B., Hunt, H. F., and Nicodemus, R. E.*: West. J. Surg. 45: 486, 1937. (36) *Patterson, W. B.*: West. J. Obst. & Gynec. 47: 273, 1939. (37) *Grumbrecht, P., and Loeser, A.*: Klin. Wchnschr. 17: 233, 1938. (38) *Tanioka, T.*: Jap. J. Obst. & Gynec. 19: 531, 1936. (39) *Tanioka, T.*: Jap. J. Obst. & Gynec. 19: 541, 1936. (40) *Hooker, D.*: The Research Publications of the Ass'n for Research in Nervous and Mental Disease 19: 237, 1939. (41) *Peiper, A.*: Monatschr. f. Kinderh. 29: 236, 1925. (42) *Ray, W. S.*: Child Development 3: 175, 1932. (43) *Spelt, D. K.*: In a paper presented at the meeting of the American Psychological Ass'n at Columbus, Ohio, September, 1938. (44) *Sontag, L. W., and Wallace, R.*: Am. J. Dis. Child. 48: 1050, 1934. (45) *Sontag, L. W., and Richards, T. W.*: Child Development No. 3: No. 4, Serial No. 17, 1938. (46) *Sontag, L. W.*: Am. J. Dis. Child. 60: 621, 1940. (47) *Richards, T. W., and Newbery, H.*: Child Development 9: No. 1, 1938.

## THE COMPLICATIONS OF IRRADIATION TREATMENT OF CARCINOMA OF THE CERVIX\*

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THIS is a study of 320 patients treated for carcinoma of the cervix during the years 1936 to 1940 inclusive, at the Ontario Institute of Radiotherapy, Toronto General Hospital, under the direction of Dr. G. E. Richards. It is almost universally true that 65 to 70 per cent of patients suffering from carcinoma of the cervix do not come for treatment until the disease has progressed to Stage III or Stage IV, so that the hope of increasing the salvage rate depends on carrying irradiation treatment to a point sometimes beyond the tolerance of the adjacent normal tissues. The complications of irradiation treatment which may result are of growing concern to all who are taking part in the treatment of patients suffering from carcinoma. Two types of reaction are met with: the acute or inflammatory, which occurs because of proximity of tissue, and the late or fibrotic, which may with extreme vascular sclerosis pass on to a state of necrosis.

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The first example of bowel injury we encountered in this series was at post mortem in 1936 when a patient dying of hemorrhage after moderately heavy high voltage therapy showed extensive ulceration of sigmoid and rectum. In 1940, however, when the high voltage depth dose was the heaviest, we have to report a number of patients who suffered intestinal injury. Two patients died from postirradiation ulcerative colitis. One of these at post mortem showed complete absence of tumor but the walls of the colon and rectum were thick and edematous, and there was complete loss of the mucosa with ulceration penetrating to the muscular coat of the bowel. Three patients died of intestinal obstruction and one of these at post mortem showed irradiation reaction of the whole intestine below the jejunum. The terminal ileum had two perforations and was bound by adhesions, and in this case also the tumor had completely disappeared.

In 1933 Behney,<sup>4</sup> in a review of antopsies in advanced carcinoma of the cervix, reported three cases which deteriorated rapidly after irradiation and died. At post mortem there was extreme sloughing of pelvic tissues and only one showed any trace of carcinoma. Death came from overwhelming intoxication probably due to too vigorous treatment. Two patients of ours who died in 1940 directly following treatment seem to correspond to this type. One had a Stage IV carcinoma and received 1,500 r. on 5 ports at 400 kv. and 3,000 r. at 180 kv. via the vaginal cone. The immediate effect was excellent. The local tumor healed and the parametrial extension was appreciably lessened. Five days later she received full radium treatment and shortly afterward began to run a fever and went rapidly downhill to die within ten weeks. Post mortem showed massive fibrosis of large and small intestine, ulcer of rectum and necrosis of vagina, a pelvic abscess in the center of the adherent mass. The only remains of tumor were small microscopic islands. The second patient also had Stage IV with rectovaginal fistula. She died three days after completing high voltage at 400 kv. 1,800 r. on 3 posterior ports and 2,100 r. on 2 anterior ports. Post mortem showed sloughing of the whole upper two-thirds of the vagina, fibrosis and thickening of the pelvic cellular tissue, bilateral hydronephrosis and hydro-nephrosis. All trace of a pre-existing tumor was gone.

Two patients, who still survive, also presented interesting histories. The first, treated in 1939, developed a tender mass in the right lower abdomen fifteen months later. Shortly after, there was a discharge of pus from the vagina and, because the mass was in the appendiceal region, a laparotomy was performed and a postirradiation adherent fibrosis of cecum and terminal ileum with abscess formation was found, apparently the result of necrosis. No evidence of active tumor was seen. The second, after high voltage therapy at 400 kv. to give 1,800 r. on 6 ports and 3,000 r. per vaginal cone at 180 kv., received 7,340 mg. hr. of radium by the Regaud method. Considerable difficulty was experienced in dilating the cervix, and this may have been the factor which caused the development of massive postirradiation cellulitis. Consequently, intestinal obstruction developed, but after an extremely severe illness, the Miller-Abbott tube and Wangenstein drainage, in the hands of a persistent resident, were successful.

danger of streptococcal infection. In the last five years, cultures have been taken from 243 patients, and of 47 with positive hemolytic streptococcal culture, 25 developed some complication subsequently, such as excessive pyrexia, vaginitis, pyometria, cellulitis, thrombophlebitis, pelvic abscess, peritonitis and septicemia. Recognizing this danger, we altered the order of treatment, high voltage therapy being given before radium. As a result, it was observed that 14 patients of the remaining 22 developed negative streptococcal culture during the preliminary treatment. This left a small group of 8 patients in whom trouble did not develop in spite of a positive culture. Other mishaps prompted the routine of anaerobic culture. Of 176 patients having such cultures taken, 72 showed positive anaerobic streptococcal culture and 32 of these developed inflammatory complications. This suggests that the anaerobic organism is more frequently present in the cervix and vagina but is not so pathogenic. The cultures from 129 patients were negative and only 28 of these developed any inflammatory complication. In all, 4 of the 5 deaths attributed to treatment prior to 1940 were due to postoperative infection, following the introduction of intrauterine radium. Three of these patients died of peritonitis and one of septicemia.

The rectum is the most exposed to injury from irradiation of any part of the intestinal tract. The frequency with which postirradiation proctitis is encountered has already been suggested. It is a condition which ordinarily disappears within a few weeks and as a rule is not followed by more serious and chronic sequelae. The typical late irradiation lesion is rectal ulceration. The late T. F. Todd,<sup>1</sup> of Manchester, wrote an excellent description of this condition outlining the two types, intrinsic, that is primary chronic ulceration of the rectum, or extrinsic which is characterized by massive perirectal cellulitis and stenosis of the rectum as a result of which ulceration develops. He recalled the term "pseudocarcinoma of the rectum," a condition which in our experience has necessitated biopsy a number of times to establish the diagnosis.

Eleven of the 36 patients treated in 1936, when massive doses of radium were given, developed primary proctitis. In 1937, 1938, and 1939, when the high voltage irradiation was increased and the radium fractionated, this complication was relatively less common, but late ulceration became more frequent. In all, 12 patients have had rectal ulceration, half of them with associated cellulitis and stenosis. The longest period between treatment and ulceration was two years. One patient required colostomy and another bled so profusely that her hemoglobin went down to 15 per cent.

Pemberton,<sup>2</sup> in a paper published in 1932, described irradiation injury primarily as an injury to the mucous membrane, generally occurring at fixed points, such as the rectum, sigmoid, and cecum, and to the small intestine when adherent. Stenosis often follows. T. E. Jones<sup>3</sup> warns that one should always keep in mind the possibility that symptoms simulating intestinal obstruction several months or years after irradiation are due to stricture rather than metastases and that investigation should be thorough before high voltage therapy is given. One patient treated by us last year suffered because the significance of these symptoms was not appreciated.

## THE INCIDENCE OF HYPERTENSION AFTER THE TOXEMIAS OF PREGNANCY

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THERE has been considerable difference of opinion regarding the subsequent effects of the hypertensive toxemias upon the maternal organism. The statement has been made that eclampsia never recurs, and that if the patient survives the acute disease, all of the signs and symptoms disappear promptly after delivery, that there are no subsequent ill effects, and that future pregnancies will not be complicated by a repetition of the toxemic signs and symptoms, or convulsions. On the other extreme, it has been occasionally intimated that the toxemic patient should never have subsequent pregnancies, because of the danger of a recurrence of the toxemia even possibly in a more serious form than with the previous pregnancy. It is likely that neither of these extremes is correct, for while some individuals may have a complete disappearance of all abnormal signs and symptoms after delivery and remain perfectly well without abnormal findings, and pass through subsequent pregnancies without any evidence of toxemia, there are others who show persisting hypertension after the toxemia and who have a recurrence of toxemic signs and symptoms even in a more severe form in following pregnancies. It is probable that the differences in these extremes are due to differences in etiology and in the underlying pathologic processes, but it is difficult to distinguish these differences unless the conditions existing before the pregnancy are known, as for example previously recognized essential hypertension or chronic nephritis, although either of these may first make their appearance during the course of a pregnancy.

In an effort to determine in our own clinic the frequency with which the hypertensive toxemias are followed by permanent hypertension, we have during the past several years attempted a follow-up study of these individuals. An effort was made to examine and study all living patients in whom a diagnosis of toxemia of pregnancy was made between January, 1925, and December, 1936, a period of twelve years. In all patients included in the study, at least one year had elapsed since the toxemia occurred and in over one-half of them five or more years had elapsed.

At the beginning of the study various tests for renal function and chemical determinations of the nonprotein nitrogenous constituents of the blood and eye ground examinations were carried out, but it was soon found that the most significant finding by which to determine the subsequent effects of the toxemia was the blood pressure determination. We have classified as hypertension, on the basis of repeated blood

It is often difficult to decide the true nature of urinary tract complications. Distortion of the base of the bladder with displacement of the ureteral openings is commonly observed, even when the tumor is entirely confined to the cervix. As a consequence, the evacuation of the bladder may be interfered with and the flow of urine from the ureters obstructed. Therefore, cystitis is not uncommon and hydroureter and hydronephrosis occur many times in the absence of symptoms. As disease progresses and the cellular tissues become involved either by invasion by tumor or by associated cellulitis, the tendency toward ureteral obstruction is much greater. As long ago as 1858, Wagner noted that ureteral dilatation was present in one-third of the individuals examined post mortem. Seventeen, of the 24 autopsies held on patients in this series of cases, showed ureteral obstruction, hydroureter and hydronephrosis or pyonephrosis. In every case, the obstruction was due to malignant infiltration of the cellular tissue. We have not encountered stricture of the ureter in a "cured" case of carcinoma of the cervix when it was not present before treatment was undertaken.

Late ulceration of the bladder is very similar to the ulceration of the rectum. We had had three cases late in onset, eighteen months to two years after irradiation. Clinical manifestations are dysuria and frequency with hematuria. The ulceration is very hard to differentiate from malignant necrosis and biopsy was required in every case.

One is impressed with the need for thorough examination of the urinary tract in all cases. A number of times cystoscopic examination has discovered secondary carcinoma of the bladder and so changed the classification of tumor to Stage IV. Pyelograms are indicated in those cases where difficulty is experienced in catheterization of the ureters. We take a nonprotein nitrogen routinely on our patients and have been surprised to find that, apart from impending uremia, it is rare to see the level above normal. We are intending to use the two-hour test as the criterion of damage to kidney function. By this routine, the condition of the urinary tract prior to treatment will be established.

Six of our patients developed vesicovaginal fistula. Our experience has been that of Graves,<sup>5</sup> Cutler, Smith and others that bladder fistula in carcinoma of the cervix is a manifestation of progressive disease. Eight patients developed rectovaginal fistula, and we felt this also was due to invasive tumor.

In 1927, Baensch of Leipzig reported the first case of spontaneous fracture of the neck of the femur following roentgen treatment of carcinoma of the cervix. The number of cases reported in the literature has increased until in a recent publication Strauss and McGoldrick<sup>6</sup> were able to collect 59. The incidence of this serious complication is variable. Dalby, Jacox and Miller<sup>7</sup> reported, in 1936, 14 cases which they had personally observed, while many men of experience have not encountered it or state the incidence as low as one in a thousand or one in two thousand treated cases.

The pathologic features of spontaneous fracture of the neck of the femur are that it develops in the superior portion of the head of the femur close to the neck as a result of vascular sclerosis with consequent osteoporosis. There is no new bone formation and secondary carcinoma

is not found at the site of fracture. Clinically, the condition manifests itself on an average of seven months postirradiation. The actual fracture is preceded by pain in the hip radiating into the thigh and knee. The diagnosis is made by x-ray.

The average age of the patients reported by Dalby and his associates was fifty-seven years. Bilateral fracture occurred in three cases. Eight of their 14 patients had metastatic involvement of the bony pelvis or the other femur. After ten months, x-ray showed 9 patients with fibrous union sufficient to allow partial function but none showed callous formation.

Strauss and McGoldrick suggest that lateral fields are largely responsible for the accident, but it is interesting to note that in the large series of Dalby, Jacox, and Miller the high voltage therapy was at 200 kv. and on 2 anterior and 2 posterior ports to give from 1,500 r. to 2,000 r. per port.

None of our patients in this series of cases experienced spontaneous fracture of the femur.

We have included 17 cases of carcinoma of the cervix which developed at least two years after supravaginal hysterectomy. It is encouraging that the salvage rate in this type of case promises to be considerably higher than when treatment is given for carcinoma of the cervix with the body in situ. This is in keeping with the results reported from other clinics.<sup>8, 9</sup> It has been suggested that there was more risk of injury to adjacent tissues in treating carcinoma of the stump of the cervix. For example, there is always the possibility of adherent intestine after abdominal operation. Our series of cases has been entirely free of major complications.

#### CONCLUSIONS

1. If a lethal irradiation dose is to be delivered to carcinoma wherever it may be, whether in the primary site or extending out widely into the pelvis, there is always the danger of irradiation beyond the tolerance of adjacent normal tissue.

2. In the treatment of carcinoma of the cervix by surgery, certain complications are accepted as frequently associated with this form of treatment. Is it not reasonable to accept some of the complications which have been described as part of the risk in the treatment of advanced cases which are quite beyond the scope of any other form of treatment?

3. The lesson to be learned from an appreciation of these complications is that we are feeling our way toward an ideal method of irradiation treatment and must be guided by our failures as well as by our successes.

#### REFERENCES

- (1) Todd, T. F.: Surg., Gynec. & Obst. 67: 617, 1938.
- (2) Pemberton, F. A.: AM. J. OBST. & GYNEC. 24: 552, 1932.
- (3) Jones, T. E.: Ibid. 29: 309, 1935.
- (4) Behney, C. A.: Ibid. 26: 608, 1933.
- (5) Graves, R. C., Kirkham, C. J. E., and Nathanson, I. T.: Surg., Gynec., Obst. 63: 785, 1936.
- (6) Strauss, H., and McGoldrick, J. L.: AM. J. OBST. & GYNEC. 41: 915, 1941.
- (7) Dalby, R. G., Jacox, H., and Miller, N. F.: Ibid. 32: 50, 1936.
- (8) Ward, G. G.: Ibid. 41: 660, 1941.
- (9) Behney, C. A.: Ibid. 40: 780, 1940.

# ANHYDRO-HYDROXY-PROGESTERONE IN THREATENED INTERRUPTIONS OF PREGNANCY

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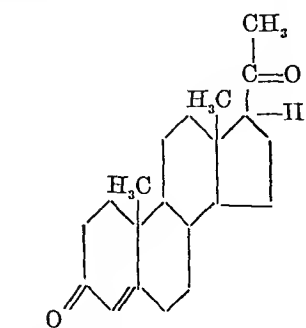
**M**ANY factors must be considered in any careful study of spontaneous abortion or miscarriage. On the part of the mother, local and constitutional physicial abnormalities, derangements of the nervous system and the emotional state and deficiencies or dysfunctions of the endocrine system must be evaluated. Variations from normal in embryologic development, which includes errors in implantation and growth or fetal deaths for a variety of reasons, must be realized also as factors of importanee.

Maintaining a constant realization that all of the aforementioned factors must be taken into consideration in possible therapeutie prevention of abortion, it is the purpose of this paper to diseuss the results of a series of threatened interruptions of early pregnancy treated with anhydro-hydroxy-progesterone.

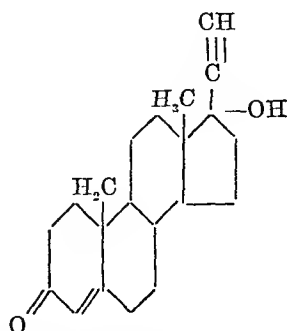
The role of the corpus luteum and its hormones in the eyele of the development of the human ovum and in the physiology of nidation and development of the fertilized ovum, is generally well understood. The clinical use of corpus luteum extracts and progesterone has been discussed by Falls, Laekner and Krohn,<sup>1</sup> Kane,<sup>2</sup> Elden,<sup>3</sup> and Campbell and Sevringhaus.<sup>4</sup> The general consensus of opinion of these observers is that progesterone therapy is of unquestionable value in the treatment of threatened abortion. However, Hamblen<sup>5</sup> in a recent article reported the results of a series of patients with histories of repeated abortions. These patients were treated with progesterone alone or with progesterone and estrogens, or progesterone and chorionic gonadotropins or anhydro-hydroxy-progesterone. He concludes that "this therapy fails to prevent abortion. There is a likelihood that large doses of progesterone may precipitate abortion by depressing intrinsic progestin."

The desirability of an oral preparation is obvious. Progesterone itself must be administered by injection, because it is practically inactive when given orally. Hohlweg and Inhoffen<sup>6</sup> succeeded in modifying the molecule so that a compound was obtained with progestin action which was effective when given by mouth.

The formulas of progesterone and of the new compound are given for comparison :



Progesterone



Anhydro-hydroxy-progesterone



It will be noted that the modifications of the progesterone formula consist of attachment of a hydroxyl group directly to carbon atom-17 and the removal of the elements of water from the acetyl group. On this account the compound is termed anhydro-hydroxy-progesterone. Another chemically descriptive term is pregnen-in-ol-17-on-3.

## OBSERVATIONS

A series of 26 cases of threatened miscarriage is reported. In 16 of the patients in this series, the threatened interruption of pregnancy was associated with bleeding. Twelve of these patients with bleeding carried on to term with successful delivery. Four miscarriages occurred.

In 4 of the patients in this series, the threatened miscarriage was not associated with bleeding, but painful uterine contractions were present. Clinically the diagnosis was justified. In none of these patients was the pregnancy terminated prematurely.

Great care has been exercised to limit the diagnosis of "threatened abortion" in this series. Many patients with low abdominal pain or discomfort simulating "pre-menstrual tension" have been treated with oral progesterone but are not included.

In an effort to evaluate therapy without reservations, additional medications and procedures were minimized. Bed rest with bathroom privileges was advised. A mild barbiturate was usually prescribed for sleep at night. Laxatives and cathartics were prohibited. A light diet was given. The use of narcotics, heavy barbiturate sedation, ice bags, and elevation of the foot of the bed were omitted.

Many of these patients were receiving thyroid at the time of onset of symptoms. In such cases, the thyroid dosage was not changed.

TABLE I. TIME OF THREATENED INTERRUPTIONS OF PREGNANCY

GESTATION IN WEEKS	NUMBER OF CASES
4	1
6	1
8	7
10	1
12	3
14	1
16	2
20	4
At time of expected menstrual period	17
Not at time of expected menstrual period	9

TABLE II. PARITY OF PATIENTS WITH THREATENED MISCARRIAGE

Primigravida	12
Gravida II with previous normal course	1
Gravida II with previous bleeding or miscarriage	2
Gravida III with previous normal course	1
Gravida III with previous miscarriage	2
Gravida IV with previous normal course	1
Gravida IV with previous miscarriage	1

It is noted from Table I that 17 of 20 patients presented symptoms of threatening miscarriage at approximately the time of an expected

menstrual period. Thirteen of the 20 cases occurred at or before the twelfth week of gestation.

Twelve of the 20 patients were primiparas. Of the 8 multiparas, 5 had had at least one previous miscarriage and might be considered as possible habitual abortion cases (Table II).

Each of these patients had already had a physical examination. Blood pressure, urine examination, blood counts, Wassermann or Kahn test and basal metabolism had been performed in all instances as part of our routine work-up.

### RESULTS

A series of 20 patients with threatened spontaneous interruption of early pregnancy were treated with anhydro-hydroxy-progesterone and progesterone. Sixteen of the 20 pregnancies (80 per cent of the cases) were maintained to successful delivery at or close to term.

Thirteen of the 20 patients in this series were treated with oral anhydro-hydroxy-progesterone. The dosage varied from 30 to 100 mg. per day and was continued for various periods of time from three days to several weeks. Seven of the patients received combined oral anhydro-hydroxy-progesterone and hypodermic progesterone.

No set rule has been offered for such therapy, and when facing a threatened miscarriage, large amounts of progesterone may be administered without untoward results. In one case, 65 mg. of intramuscular progesterone and 560 mg. of anhydro-hydroxy-progesterone were administered in nineteen days followed by 10 mg. of the orally effective preparation twice a day for three weeks. This pregnancy continued after what was first considered an inevitable abortion.

It is our belief that if sufficient oral anhydro-hydroxy-progesterone be given, it may supplant hypodermic therapy. In our experience, 60 to 100 mg. or more oral anhydro-hydroxy-progesterone in three or four split doses during the first twenty-four hours after onset of symptoms is a therapeutic amount. The usual procedure is to administer 2 to 10 mg. of progesterone intramuscularly once or twice and from there on carry on with oral anhydro-hydroxy-progesterone alone. At this time it may be propitious to emphasize the importance of onset of therapy *immediately* after onset of symptoms. Three of the patients who miscarried in this series, reported the bleeding or cramps more than twenty-four hours after their onset. In these cases, therapy was of no avail. This does not mean that they might have carried on if treatment had been started earlier. A blighted ovum may have been the cause of each case. One patient presented the problem of a bleeding polyp complicating early pregnancy.

When progesterone is being administered prophylactically as in habitual abortion or other conditions where a miscarriage might be feared, 1 mg. should be given every three or four days intramuscularly or 10 to 30 mg. daily if the orally effective preparation may suffice.

Toxic symptoms were not noted in any patient in this series.

It is difficult to evaluate the relative value of the effective oral and subcutaneous dosage of these related preparations. It is our impression that about ten times the effective subcutaneous dose of progesterone is effective when administered orally as anhydro-hydroxy-progesterone.

## DISCUSSION

There is a group of individuals not included in this series whose symptoms of low pelvic pressure, insufficient increase in size of the uterus, or temporary decrease in size and increase in irritability of the uterus, indicated a tendency toward a threatened miscarriage. However, the symptoms were not severe enough to classify these individuals as threatened miscarriage.

We have used anhydro-hydroxy-progesterone freely in numerous such cases and with pleasing results. The dosage has varied from 20 to 60 mg. daily. A marked degree of relaxation of the uterus with a rise of 2 to 4 cm. in the McDonald measurement in one week is not unusual. A concomitant improvement in the state of well-being was noted frequently.

It is realized, as mentioned previously, that this is an indefinite clinical group; one with uncertain diagnosis and one which responds well to other forms of therapy such as bed rest and mild sedation. However, the response to anhydro-hydroxy-progesterone is so marked that it is considered worthy of mention.

There has been some discussion relative to the desirability of maintaining a gestation with the prospect of an abnormal child or monstrosity. There has been no such end result in our experience to date. Our feelings are that if the ovum be blighted, it will go on to miscarriage in spite of preventive therapy.

## SUMMARY

1. Twenty patients with threatened spontaneous interruption of pregnancy were treated with anhydro-hydroxy-progesterone (oral) and hypodermic progesterone.

2. Care has been taken to limit the diagnosis of threatened miscarriage.

3. Sixteen pregnancies (80 per cent) were maintained with successful delivery at term.

4. Four patients miscarried. In each of these cases, treatment was begun more than twenty-four hours after the onset of symptoms. One of these miscarriages followed removal of a bleeding polyp.

5. Oral anhydro-hydroxy-progesterone has been administered in dosage up to 100 mg. per day. Intramuscular dosage of progesterone varied from 1 to 30 mg. per day.

6. Anhydro-hydroxy-progesterone\* seems to prove to be a valuable medication in the treatment of threatened spontaneous miscarriage.

7. No toxic symptoms were noted.

## REFERENCES

- (1) Falls, F. H., Lackner, J. E., and Krohm, L.: J. A. M. A. 106: 271, 1936.
- (2) Kane, H. F.: AM. J. OBST. & GYNEC. 32: 110, 1936. (3) Elden, C. A.: Ibid. 35: 648, 1938. (4) Campbell, R. E., and Sevringhaus, E. L.: Ibid. 39: 593, 1940. (5) Hamblen, E. C.: Ibid. 41: 664, 1941. (6) Hohlweg and Inhoffen: Die Naturwissenschaften 26: 96, 1938.

\*The preparation, marketed as "pranone," was supplied by Dr. Max Gilbert of the Schering Corporation.

# ORAL THERAPY WITH PREGNENINOLONE IN FUNCTIONAL UTERINE BLEEDING

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**F**UNCTIONAL uterine bleeding is excessive bleeding due to factors which are not yet known. Many theories and therapeutic agents have been recommended, but none turned out to be entirely satisfactory. One factor, however, seems to be present for uterine bleeding, whether normal or abnormal, namely estrogen stimulation. However, the future may prove the existence of some relationship between the hormones and structural changes in the endometrial vascular supply and that the factors which are responsible for the bleeding are within the endometrium, possibly of vascular nature, and not dependent upon the histologic type of the endometrium.

## MATERIAL

This study was conducted on a series of 20 cases of functional uterine bleeding, in which any palpable organic disease could be excluded. According to the clinical type of bleeding, they can be subdivided into 11 cases of puberty bleeding and 9 cases of maturity bleeding.

## METHODS

A careful clinical evaluation of the patients, based on a thorough history, physical examination, appropriate laboratory studies and endometrial biopsies was carried out. A quantitative estimation of urinary prolans and estrogens was made in all cases. The prolans were assayed in a morning specimen and the estrogens in a twenty-four-hour specimen. The urinary prolans were extracted by utilizing the modification of Zondek's method. A fresh refrigerated specimen of urine was slightly acidified with dilute acetic acid. Ethyl alcohol was added and the mixture allowed to stand from two to twenty-four hours, then centrifuged and the supernatant fluid discarded. Ethyl ether was added, well shaken in order to break up the precipitate, which removes the estrogenic substances, again centrifuged and the supernatant fluid discarded. The precipitate was dried until all ether had evaporated. Distilled water was added and constantly shaken for ten minutes, again centrifuged and the supernatant fluid saved, which contains the follicle-stimulating hormone. Three immature female mice weighing from 6 to 8 Gm. are injected twice daily for three days. The mice are not injected on the fourth day and are autopsied on the fifth day or one hundred hours after the first injection. The estrogens were extracted by using the Kurzrok and Ratner method. Nine hundred cubic centimeters of the twenty-four-hour urine specimen were made slightly acid with dilute acetic acid, then saturated with sodium chloride. The treated urine is then covered with ethyl acetate to the top of the flask. A second

flask is filled with 200 c.c. of ethyl acetate and attached to the first flask. The hot plate is turned on to medium heat and the ethyl acetate distilled over, and condensed. It drops to the bottom of the first flask from which it returns to the second flask. The drops of ethyl acetate in passing upward through the urine extract the hormone. This provides continuous extraction for forty-eight hours. The extracted urine is then discarded and the ethyl acetate extract, which contains the hormone, is concentrated by vacuum distillation. To the remaining substance, 6 c.c. of propylene glycol are added. This solution is then injected into ovariectomized rats. The animal assay consists of injecting a definite dosage of the solution in three equal doses, and twenty-four hours later making a vaginal smear. A positive smear must show the cornified cells characteristic of estrus.

In order to determine the effect of pregnenolone on the endometrium, pretreatment endometrial biopsies were taken, by suction curettage, and several biopsies after oral therapy in all the cases where no contraindication to take an endometrial biopsy was given.

#### DOSAGE

In 1938 Inhoffen and Hohlweg prepared a derivative of progesterone, which was identified as pregnenolone. When given orally to immature mice previously treated with estrogens, it was approximately 15 times as potent as progesterone given orally, while given by injections to similar animals, it was only one-third as effective in producing progestational changes as was synthetic progesterone. The question we were most interested in was the possibility of affecting the endometrium by oral corpus luteum hormone therapy, the dosage necessary, and the influence of our therapy on the bleeding. According to individual authors, the doses required for the conversion of a proliferative endometrium into its secretory phase are different. Kaufman uses 60 mg., Zondek 40 to 45 mg. of corpus luteum hormone by injection, while our own investigations showed the need of about 40 mg. of corpus luteum hormone. Our own data on oral pregnenolone\* therapy show that we need from 280 to 350 mg. to stop the bleeding and to obtain progestational response of the endometrium. This would mean that we need from six to seven times the injected dose when given by mouth. Similar good results in functional uterine bleeding with oral corpus luteum therapy have been reported by Clauberg, Ustuen, Wenner, and Lauterwein. Hamblen and co-workers report good results after oral use of pregnenolone in functional menorrhagia.

#### CASE REPORTS

##### *Juvenile Bleeding.*—

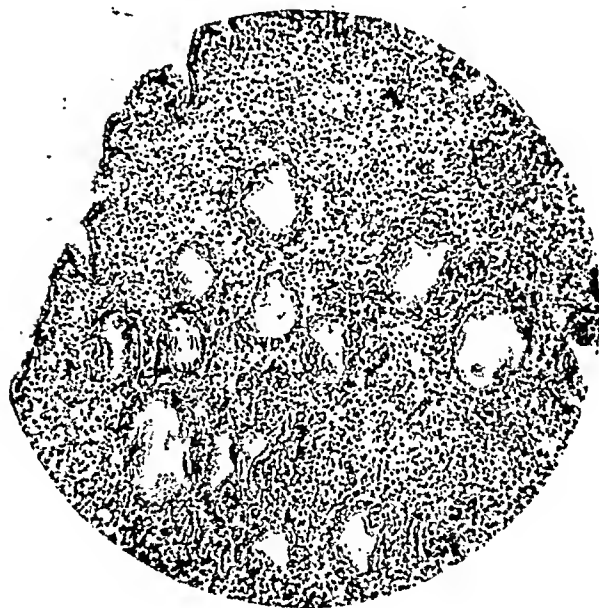
CASE 1.—A. S., a white 18-year-old girl, had episodes of menorrhagia for two years. Onset of period at 14 years of age and occurred every twenty-eight days, lasting for four or five days. A year and one-half ago curettage had been performed to check severe hemorrhage. Prior to consultation in clinic, patient bled for six weeks continuously. Genitals were normal. The endometrial biopsy showed a proliferative endometrium. Hormone determination: Estrogenic hormone 10 R.U. per day. Follicle-stimulating hormone was negative.

\*Progesterol (Brand of pregnenolone) 1 tablet = 10 mg., was supplied through the kindness of Dr. Leo Pirk of Roche-Organon, Inc., Nutley, N. J.

*Therapy:* Three hundred milligrams of pregnenolone were given over a period of six days in daily doses of 50 mg. Bleeding stopped on the fifth day. Endometrial biopsy, done on the ninth day after therapy started, showed some degree of progestational alteration. Subsequently an oral dose of 240 mg. of pregnenolone, given during the second half of the cycle, established a regular menstrual cycle for the last six months.



A.



B.

Fig. 1.—Case 2. R. H. (A) Previous periods every six to eight weeks for ten days. Now bleeding for three weeks from a proliferative endometrium. (B) 350 mg. of pregnenolone given in seven days stopped bleeding. Biopsy on eighth day showed full progestational response of the endometrium.

CASE 2.—(Fig. 1.) R. H., 18-year-old white girl, had had irregular periods since her menarche at the age of 13 years. Periods occurred every six to eight weeks for ten days. Genitals were normal. Bleeding had been present for three weeks. The endometrial biopsy showed a proliferative endometrium. Hormone determination: Estrogenic hormone 18 R.U. per day. Follicle-stimulating hormone was negative.

*Therapy:* Patient received 50 mg. of pregnenolone daily over a period of seven days, totaling 350 mg. Biopsy on the eighth day showed full progestational response of the endometrium. Regular menstrual cycles were established through a period of four months with 240 mg. pregnenolone given during the second half of the cycle.

CASE 3.—M. W., virgin, 14-year-old white girl, began to menstruate at 12 years of age. The periods were regular in the beginning, occurring every 24 days and lasting for five or six days. For the last three months, periods lasted two weeks followed by staining for one week. Genitals were normal. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. No biopsy was taken.

*Therapy:* Patient received a total of 250 mg. of pregnenolone in daily doses of 50 mg. For the following five months a menstrual cycle of twenty-six days could be established with 260 mg. of pregnenolone given in divided doses during the second half of the cycle, the bleeding lasting for four days.

CASE 4.—L. S., 15-year-old white girl, virgin; menses started at 12 years of age, occurring every 28 days and lasting for four or five days for one year, then amenorrhea for two years. She started to bleed profusely for two weeks. She was very anemic. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 18 R.U. per day. Follicle-stimulating hormone was negative.

*Therapy:* Received daily 50 mg. of pregnenolone for seven days, totaling 350 mg. Bleeding stopped after five days. During the following six months menstrual cycle occurred every thirty-five days and lasted four days without any further medication.

CASE 5.—G. L., 18-year-old white girl. Periods had occurred every twenty-eight days, lasted five to six days, and were regular, but for the last year they occurred every two months and lasted for two weeks. Genitals were normal. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. The endometrial biopsy showed a proliferative endometrium.

*Therapy:* Three hundred milligrams of pregnenolone were given for six days, daily dose 50 mg. The endometrial biopsy (taken eight days after therapy was started) showed some degree of progestational alteration. Bleeding stopped on the seventh day. Following this, patient received 260 mg. of pregnenolone during second half of cycle, whereby, for the last seven months a cycle of twenty-nine days was established.

CASE 6.—F. S., 18-year-old colored girl. The onset of the menstrual period occurred at eleven years of age. Periods had been regular, occurring every twenty-eight days, lasting four or five days. For last half year, periods had been irregular, every four or five weeks, lasting three weeks. Genitals were normal. Hormone determination: Estrogenic hormone 20 R.U. per day. Follicle-stimulating hormone nega-

pressure determinations, all patients in whom the systolic pressure was 140 mm. of mercury or more and the diastolic 90 or more.

TABLE I

	CASES	PATIENTS	DEATHS	DEATH RATE
Toxemia without convulsions	430	377	9	2%
Toxemia with convulsions	136	134	19	14%
Totals	566	511	28	4.9%

For the period under consideration there were 566 instances of hypertensive toxemia occurring in 511 patients. The toxemia had occurred more than once in the same patient in 55 instances, giving an incidence of recurrent toxemia of 10.7 per cent. Of the 511 patients, 28 died during their stay in the hospital, a mortality rate for the entire group of 4.9 per cent. Nine deaths (2 per cent) occurred in the nonconvulsive group, while 19 deaths (14 per cent) occurred in the convulsive group. Of the 483 patients who were discharged alive from the hospital, 7 were found to have died subsequently. Attempts at repeated follow-up examinations were successful in only 224 patients, a follow-up incidence of 47 per cent.

TABLE II

Patients discharged alive	483	
Died since discharge	7	
Patients not located	252	(53%)
Number with follow-up examinations	224	(47%)
Normal blood pressure at follow-up examinations	120	(53.5%)
Hypertension at follow-up examinations	104	(46.5%)

Of the 224 patients repeatedly re-examined, 104, or 46.5 per cent, had definite hypertension from one to thirteen years after the toxemia. If it may be presumed that this ratio is preserved in those who could not be re-examined, then it may be concluded that a patient with toxemia has almost a 50 per cent chance of a subsequent persistent hypertension. Blood pressure determinations of a comparable group after normal pregnancies and with similar age distribution revealed an incidence of hypertension of 12 per cent, which is approximately the average incidence of hypertension in the female during the reproductive period. So, it seems safe to assume that the toxemic pregnancy must have played a significant part in the high incidence of hypertension found in the follow-up examinations.

In an attempt to determine what factors might be present to influence the persistence of hypertension, the cases were tabulated and analyzed according to age, parity, convulsions, blood pressure levels at the time of the toxemia, and the severity of the toxemia.

TABLE III. AGE AT TIME OF TOXEMIA AS FACTOR IN RESIDUAL HYPERTENSION

AGE	TOTAL EXAMINED	HYPERTENSION	PER CENT
19 and below	62	12	19.4
20 to 24	53	18	34
25 to 29	27	15	55.5
30 to 34	37	23	62.2
35 to 39	29	23	80
40 and over	16	13	81.3

In Table III the patients are grouped into five-year age periods, and the findings clearly reveal an increased incidence of residual hypertension as the age advances. Those patients who were less than twenty years of age at the time of their toxemia only had a 19 per cent incidence of hypertension while those who were thirty-five years or more had an 80 per cent incidence.



six weeks. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 16 R.U. per day. Follicle-stimulating hormone was negative.

*Therapy:* Patient received 350 mg. of pregnenolone in divided doses over a period of seven days. Bleeding did not stop and was allowed to continue for four days. Twenty-five milligrams of corpus luteum hormone were given by injection which stopped bleeding after forty-eight hours. Since then 6 normal periods could be established with 350 mg. of pregnenolone given during the second half of the cycle.

*Maturity Bleeding.—*

CASE 12.—D. E., 28-year-old white patient, had been married eight years and had never become pregnant. Onset of period occurred at fourteen years of age, and recurred every twenty-eight days, lasting four or five days. Periods were completely irregular for three years, alternating between amenorrhea and profuse bleeding. She has been bleeding for six weeks. Genitals: No pathology. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. The endometrial biopsy showed a cystic and glandular hyperplasia.

*Therapy:* Patient received 350 mg. of pregnenolone in divided doses over a period of seven days. Bleeding stopped on sixth day. Endometrial biopsy ten days later showed some progestational alteration. Normal cycles for four months could be maintained with 260 mg. given in the second half of the cycle. Biopsies revealed that bleeding occurred from a very early secretory endometrium.

CASE 13.—A. G., 24-year-old white patient. The onset of the menstrual period began at 13 years of age, occurred every thirty-two days and lasted four or five days. For the last four months patient had bled for ten days followed by staining for twelve days. Genitals were normal. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. The endometrial biopsy showed a cystic and glandular hyperplasia.

*Therapy:* Patient received for seven days 50 mg. of pregnenolone, totaling 350 mg. Biopsy on the tenth day revealed a proliferative endometrium. For the next three months, patient received 200 mg. orally in the second half of the cycle. Biopsies revealed some degree of progestational alteration.

CASE 14.—F. H., 35-year-old white patient. The menstrual period began at fourteen years of age, occurred every twenty-eight days, and lasted four or five days. Since her last pregnancy, starting with the first period, 6 weeks post partum, patient bled continuously for seven weeks. Genitals were normal. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. The endometrial biopsy showed a cystic and glandular hyperplasia.

*Therapy:* Patient received 280 mg. of pregnenolone over a period of seven days in daily doses of 40 mg. Bleeding stopped on fifth day. Biopsy on ninth day revealed a proliferative endometrium. For the last four months a thirty-two-day normal menstrual cycle could be maintained with 280 mg. of pregnenolone. Biopsies taken premenstrually showed an early secretory endometrium.

tive. The endometrial biopsy showed a cystic and glandular hyperplasia.

*Therapy:* Patient received 350 mg. of pregnenolone in divided doses over a period of seven days. Bleeding stopped on the sixth day. The endometrial biopsy showed, on the twelfth day, a proliferative endometrium. With 260 mg. of pregnenolone a menstrual cycle of five weeks could be established.

CASE 7.—M. Sp., 17-year-old white virgin. Menstrual periods began at fifteen years of age, occurring every thirty-six to forty days and lasting three days. For last four months periods occurred every twenty-three days, lasting twelve days. Rectal examination: No pathology. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. No biopsy.

*Therapy:* Patient received 300 mg. of pregnenolone in divided doses for six days. Bleeding stopped on the fourth day. Normal cycle has continued for three months without therapy. Regular.

CASE 8.—R. W., 14-year-old white virgin. Her first period was a continuous bleeding for six weeks. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 14 R.U. per day. Follicle-stimulating hormone was negative.

*Therapy:* Patient received 350 mg. of pregnenolone in divided doses over a period of seven days. Bleeding stopped on the fifth day. She had her second regular period with 240 mg. of pregnenolone given during second half of cycle.

CASE 9.—M. W., 17-year-old white virgin. First period started when patient was 16 years; then complete amenorrhea until four weeks ago when she started to menstruate which has continued until present time. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 20 R.U. per day. Follicle-stimulating hormone was negative.

*Therapy:* Patient received 350 mg. of pregnenolone in divided doses over a period of seven days. Oral therapy did not influence bleeding and on account of severe anemia (hemoglobin 40 per cent) corpus luteum hormone total of 40 mg. in 2 doses was given by injection, which stopped bleeding in seventy-two hours. Further menstrual periods could be obtained with oral pregnenolone medication, 350 mg. during the second half of cycle.

CASE 10.—J. St., 13-year-old white virgin. First menstrual period started three weeks ago, and patient is still bleeding. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 8 R.U. per day. Follicle-stimulating hormone was negative.

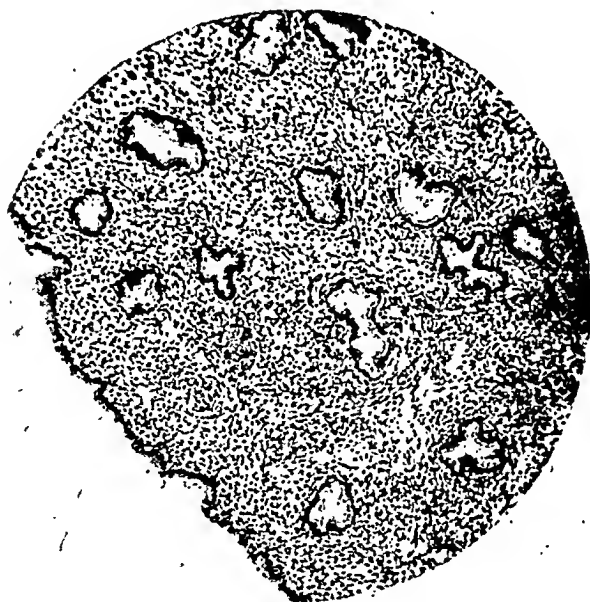
*Therapy:* Patient received 100 mg. of pregnenolone daily over a period of three days without any effect on the bleeding. General condition poor. (Hemoglobin 45 per cent.) She received 50 mg. of corpus luteum hormone by injection which stopped bleeding after last injection. Five normal periods were established since then by oral pregnenolone therapy, 350 mg. during second half of cycle.

CASE 11.—L. B., 15-year-old colored virgin. The onset of menstrual periods occurred at 13 years of age. She had two normal periods and became amenorrheic for twenty-one months. Patient is bleeding now for

taken on the fourteenth day showed a secretory endometrium. She had regular periods every thirty-two days for seven years for the last five months, with 280 mg. of pregnenolone given during the second half of cycle. Several premenstrual biopsies revealed secretory endometrium.



A.



B.

Fig. 2.—Case 18. H. G. (A) The menstrual periods began at 15 years of age, occurred every thirty-two days and lasted for five or six days. For one year menstrual period every eight weeks; actual bleeding for three weeks. Now bleeding from a proliferative endometrium. Three hundred and fifty milligrams of pregnenolone in seven days stopped bleeding on tenth day. (B) Biopsy on fourteenth day showed secretory endometrium.

CASE 15.—L. C., 32-year-old white patient. The menstrual period began at age of fourteen years, occurred every twenty-six to twenty-eight days, and lasted five days. She had spontaneous deliveries in 1932 and 1939. Following the last delivery in 1940, she had two normal periods, twenty-eight days apart. Her third period post-partum lasted for three weeks. The endometrial biopsy showed a cystic and glandular hyperplasia. Hormone determination: Estrogenic hormone 8 R.U. per day. Follicle-stimulating hormone was negative.

*Therapy:* Fifty milligrams of pregnenolone were given daily for seven days, totaling 350 mg. Bleeding stopped after six days of therapy. Biopsy taken on the tenth day showed a proliferative endometrium. A twenty-eight-day cycle could be obtained for four months with 240 mg. of pregnenolone given in the second half of the cycle. Biopsies taken premenstrually showed some progestational alteration.

CASE 16.—E. L., 24-year-old colored patient. Onset of period occurred at twelve years of age. Period from the beginning was irregular. She was amenorrheic up to six months. Since patient was married, four years ago, periods have occurred every thirty-two to thirty-six days, lasting five days. She has never been pregnant. For last half year, menstrual bleeding has occurred for twelve days followed by staining for another 14 days. The endometrial biopsy showed a proliferative endometrium. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative.

*Therapy:* Fifty milligrams of pregnenolone were given for six days, totaling 300 mg. Bleeding stopped after five days. Biopsy taken on the eighth day showed early progestational phase. Endometrial biopsies taken premenstrually for six months showed full progestational development.

CASE 17.—B. W., 26-year-old white patient. The menstrual period began at the age of thirteen, occurred every twenty-eight days and lasted four or five days. She menstruated regularly until she had a child early in 1940. The first menstrual period after the delivery lasted for two weeks, with profuse bleeding; then she menstruated every eighteen days for two weeks. The endometrial biopsy showed an early secretory endometrium. Hormone determination: Estrogenic hormone 18 R.U. per day. Follicle-stimulating hormone was negative.

*Therapy:* Forty milligrams of pregnenolone were given for a period of seven days, totaling 280 mg. Bleeding stopped on the ninth day. Biopsy taken on the twelfth day showed a secretory endometrium. With a monthly dose of 250 mg. of pregnenolone a regular 30-day cycle could be established for the following 5 months. Several premenstrual biopsies taken showed a secretory endometrium.

CASE 18.—(Fig. 2.) H. G., 23-year-old white girl. The menstrual period began at fifteen years of age, occurred every thirty-two days, and lasted for five or six days. For one year, menstrual periods occurred every eight weeks; actual bleeding for three weeks. The endometrial biopsy showed a proliferative endometrium. Hormone determination: Estrogenic hormone 8 R.U. per day. Follicle-stimulating hormone was negative.

*Therapy:* Fifty milligrams of pregnenolone were given for seven days, totaling 350 mg. Bleeding stopped on the tenth day. Biopsy

2. The bleeding factors seem to be vascular within the endometrium and not dependent upon the histologic type of the endometrium.

3. Functional uterine bleeding can be controlled by oral use of pregnenolone, the effective dose ranging between 280 and 350 mg. given in daily doses of 50 mg.

4. From 6 to 7 times the amount of pregnenolone by weight is required orally as compared with progesterone when given by injection.

5. Three patients with juvenile bleeding did not respond to oral therapy and received from 25 to 50 I.U. of corpus luteum hormone by injection, which stopped the bleeding in from 48 to 72 hours.

6. Two cases showed complete progestational changes of the endometrium.

7. Normal menstrual cycle can be maintained with smaller doses (200 to 240 mg.) when given in the second half of the cycle.

8. Further studies are necessary to evaluate the minimum dosage for controlling the bleeding and the maintenance of a regular menstrual cycle.

I am indebted to Dr. Benjamin P. Watson, Director, Department of Obstetrics and Gynecology, Sloane Hospital for Women, for constant encouragement and advice, and for his placing the material of the Sloane Hospital for Women and the Vanderbilt Clinic at my disposal.

#### REFERENCES

1. *Anspach, B. M., and Hoffman, J.*: AM. J. OBST. & GYNEC. 28: 473, 1934.
2. *Barilemez, G. W.*: *Physiol. Rev.* 17: 28, 1937.
3. *Claiberg and Ustuen*: *Zentralbl. f. Gynäk.* 32: 1745, 1938.
4. *Engle, E. T., Smith, P. E., and Schelesnyak, M.*: AM. J. OBST. & GYNEC. 29: 787, 1935.
5. *Engle, E. T.*: *Ibid.* 38: 600, 1939.
6. *Hamblen, E. C.*: *Endocrinology* 24: 13, 1939.
7. *Hamblen, E. C., and Zow*: *Endocrinology* 26: 201, 1940.
8. *Inhoffen, H. W., and Hohlweg, W.*: *Naturwiss.* 26: 96, 1938.
9. *Jeffcoate, T. H. A.*: *J. Obst. & Gynaec. Brit. Emp.* 44: 31, 1937.
10. *Lauterwein*: *Zentralbl. f. Gynäk.* 3: 108, 1940.
11. *Salmon, Walter, and Geist*: *Proc. Soc. Exper. Biol. & Med.* 40: 252, 1940.
12. *Smith, G. V. S., and Smith, O. W.*: AM. J. OBST. & GYNEC. 36: 769, 1938.
13. *Wenner, Robert*: *Schweiz. med. Wchnschr.* 70: 417, 1940.
14. *Wilson, L., and Kurzrok, R.*: AM. J. OBST. & GYNEC. 31: 911, 1936.
15. *Zondek, B., and Rozin*: *Lancet* 1: 504, 1939.
16. *Zondek, B., Rozin, and Vesell*: AM. J. OBST. & GYNEC. 40: 391, 1940.

23 EAST SEVENTY-FOURTH STREET

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Macknight, Ella: Almost Complete Occlusion of the Vaginal Orifice Following Childbirth, *Med. J. Australia* 2: 699, 1940.

The author reports a case of almost complete occlusion of the introitus due to formation of a septum by adhesions of both labia minora. The septum varied between one-fourth and one-half inch in thickness. It developed after the birth of a premature (8 mo.) baby eighteen months previously. Coitus was impossible, but menstruation had been normal. There was no difficulty with micturition.

WILLIAM BERMAN

CASE 19.—M. B., 32-year-old white girl. The menstrual period began at 15 years of age, occurred every twenty-three days, and lasted for four days. Her first 3 periods after her last delivery lasted for two weeks. Patient has been bleeding profusely for three weeks. Genitals were normal. Hormone determination: Estrogenic hormone 8 R.U. per day. Follicle-stimulating hormone was negative. The endometrial biopsy showed a cystic and glandular hyperplasia.

*Therapy:* Patient received 350 mg. of pregnenolone over a period of seven days in daily doses of 50 mg. Bleeding stopped on the tenth day. Biopsy on the twelfth day revealed a proliferative endometrium. For the last six months a normal menstrual cycle could be maintained with 220 mg. of pregnenolone. Biopsies taken premenstrually showed an early secretory endometrium.

CASE 20.—L. R., 20-year-old white girl. Her menstrual period began at 14 years, occurred every twenty-six days, and lasted for four or five days. For the last two years, periods occurred every five or six weeks; she has been bleeding continuously for seven weeks. Genitals were normal. Hormone determination: Estrogenic hormone 16 R.U. per day. Follicle-stimulating hormone was negative. The endometrial biopsy showed a proliferative endometrium.

*Therapy:* Fifty milligrams of pregnenolone for a period of seven days; totaling 350 mg. Bleeding stopped on the twelfth day. Biopsy taken on the thirteenth day showed an early secretory endometrium. With a monthly dose of 240 mg. of pregnenolone a regular twenty-eight-day cycle could be established for the last four months. Several premenstrual biopsies showed a secretory endometrium.

#### COMMENT

Pregnenolone was very well tolerated by all our patients. The highest daily dose was 50 mg., totaling up to 350 mg. over a period of seven days; only one patient received 100 mg. daily for three days, totaling up to 300 mg. In 13 cases endometrial biopsies were obtained. The first biopsy was always taken before treatment was started, the second biopsy after therapy was effective and further biopsies for several months always from three to five days premenstrually. Biopsies taken before treatment was started showed in 6 cases proliferative endometrium, in 6 cases cystic and glandular hyperplasia, and in one case early secretory endometrium. Biopsies taken from eight to fourteen days after treatment had started, showed in 5 cases some degree of progestational endometrium, in 3 cases a generalized progestational response of the endometrium and in 5 cases a proliferative endometrium. Three cases of juvenile bleeding did not respond to oral therapy and received from 25 to 50 I.U. corpus luteum hormone by injection, which stopped bleeding from 48 to 72 hours after the injections were given. Regular menstrual cycles could be established with reduced medication, 200 to 240 mg. when given orally in the second half of the cycle.

#### CONCLUSIONS

1. Functional uterine bleeding may be due to a relationship between hormones and structural changes in the endometrial vascular supply.

unless there is superimposed upon it the high contractions of corpus luteum influence. One may conclude, therefore, that two conditions are usually present in primary dysmenorrhea; namely, tetany plus high amplitude contractions.

#### TECHNICAL PROCEDURE

Fifteen patients who suffered severely with each menses and in whom no pelvic pathology could be demonstrated were chosen for this study. Their ages varied from sixteen to twenty-six; the average age was twenty-one. Nine were nulliparas. Nine were married and 4 were

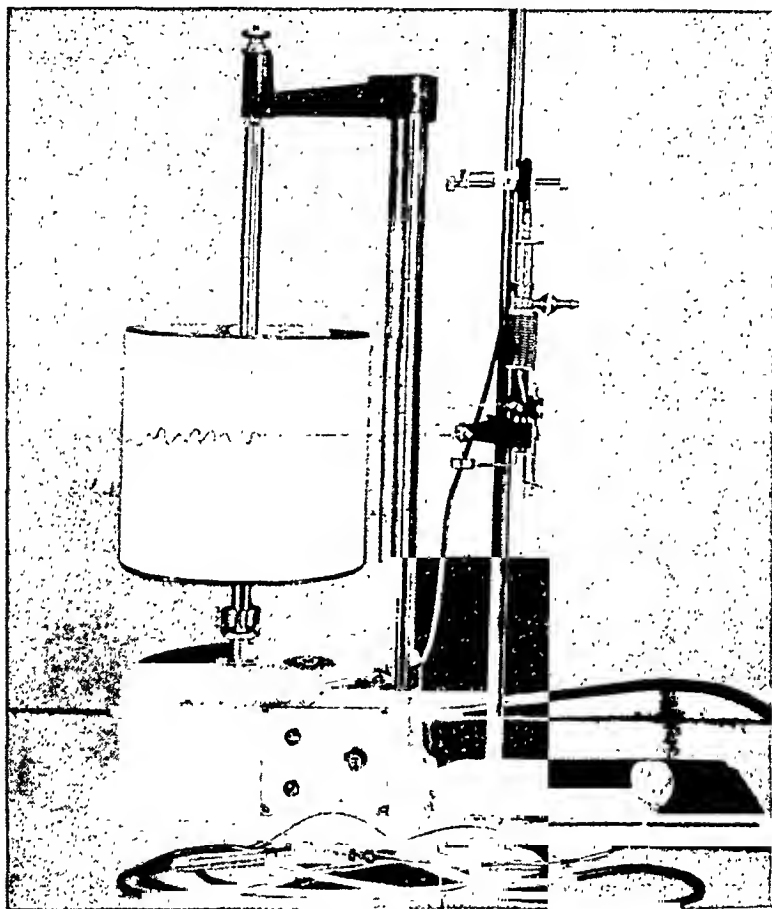


Fig. 1.—The distended balloon connected through a closed water system to the mechanical ink recorder. The electric kymograph is equipped with a timer.

virgins. All of the patients menstruated on cycles from twenty-four to thirty-two days. Their cooperation was obtained by explaining to them that the procedure was an attempt to find the cause of their dysmenorrhea.

A small condom balloon attached to a flexible metal cannula was placed in the uterine cavity after dilating the cervix with a very small uterine sound. This may be accomplished with a minimum amount of discomfort to the patient. The cannula is connected by a rubber tube to a mechanical ink writer which responds through a delicate system of levers to small variations in the intrauterine pressure. The system is filled with water which transmits directly the pressure changes in the

## UTERINE CONTRACTIONS IN DYSMENORRHEA

WILLIAM BICKERS, M.D., RICHMOND, VA.

SEVERE, intermittent, cramplike pain associated with the menses is the most common cause of disability among young women. An eastern college for women reports 10 per cent of its absentee days as caused by painful menstruation. The Medical Department of one of our large industries reports that dysmenorrhea costs its company \$20,000 annually.

The clinical picture is well known to every practitioner. A young woman, usually under twenty-five years of age, comes to the doctor's office seeking his scientific advice for the alleviation of a condition which numerous highly advertised proprietary drugs have failed to relieve. She gives a history of acute, spasmodic pain with the menses which usually dates from puberty. Pelvic examination reveals no pathology. This is the primary type of dysmenorrhea. There is a second group, small in number, and usually in the fourth decade of life, who have fibroids, endometriosis, pelvic inflammatory disease, uterine polyp, or some other pathology to explain the acquired dysmenorrhea. This is the secondary type. The first and more important group has a physiologic dysfunction toward which this study is directed. The effect of several commonly used drugs upon this abnormal physiology is also investigated.

### PATHOLOGIC PHYSIOLOGY

The pain of dysmenorrhea arises from the intermittent contractions of the myometrium. Normal contractions of muscle fibers produce no pain; while in the absence of adequate blood supply, these contractions become acutely painful. It cannot be demonstrated that the dysmenorrheic uterus is any less well supplied with blood than the nonpainful menstruating uterus. However, this study does demonstrate the presence of tetany in dysmenorrhea as contrasted with the atony seen in the nonpainful menstrual contractions. This tetany may interfere with normal oxygenation of the myometrium. The high contractions normally present during menstruation may then cause pain. The pathologic physiology may be comparable to that of angina pectoris and that which occurs when the muscles of the forearm are exercised after a tourniquet has been applied.<sup>3</sup>

It has been shown in previous studies that uterine contractions during menstruation in a normal ovulatory cycle are characterized by relatively high amplitude, low frequency, and marked absence of tetany. The absence of tetany permits the uterus to relax between contractions, thus improving its blood supply and the contractions are painless. High amplitude contractions produce no pain, provided there is adequate relaxation. Conversely, there is no pain associated with tetany



tractions are low in amplitude, rapid, and somewhat tetanic (Fig. 2). These contractions are characteristic of unopposed estrogen influence. During the luteal phase (postovulatory), the contractions assume a much higher amplitude, lower frequency, and tetany is abolished. This is the progesterone influence. Seven tracings were taken in this group while the patient was menstruating. These nonpainful menstrual contractions show a complete absence of tetany. With this type of motility during menstruation, no pain is experienced (Fig. 2). The writing point returns to the base line after each contraction, showing complete relaxation of the uterus. These patterns of uterine motility have now been observed by several investigators. They are consistent and may be accepted as the true picture of uterine contractility in the normal ovulatory cycle.

## DYSMENORRHEA

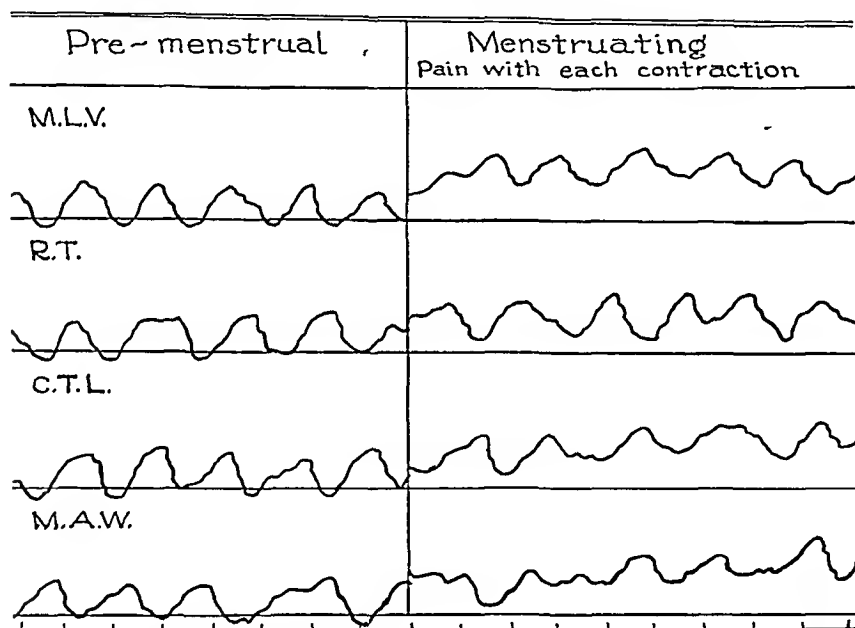


Fig. 3.—The premenstrual contractions have a relatively high amplitude, each contraction returns to the base line, and there is no tetany. The menstruating contractions are similar except they do not return to the base line because the uterus is tetanic.

## MOTILITY IN PAINFUL MENSTRUATION

In each of the 15 cases studied, a normal ovulatory cycle was found. The presence of a corpus luteum was evidenced by the high amplitude, low frequency contractions seen only when the uterus is under progesterone influence. The presence of a corpus luteum was further demonstrated by finding a secretory endometrium during the premenstrual phase in all cases. Tracings taken during the premenstrual phase on these patients with dysmenorrhea showed the usual high amplitude, low frequency, atonic type of contraction (Fig. 3). However, the tracings which were taken during menstruation on these cases, usually on the first day and while the patient was experiencing her most severe

balloon to the mechanical recorder. This has been found to be more efficient than air, because the compressibility of air may introduce some error. The writing point connected to the mechanical recorder writes the tracings of uterine contractions upon a revolving kymograph (Fig. 1).

At least two tracings were made on each patient, one during the late luteal or premenstrual phase and the other while the patient was actually menstruating and experiencing her dysmenorrhea. The tracings were permitted to run for at least thirty minutes. When a drug was administered, adequate time was allowed to observe its effect. Objections to this technique have been raised on the grounds that a foreign body distending the uterus would alter the normal patterns of uterine motility.

### NON - PAINFUL MENSTRUATION

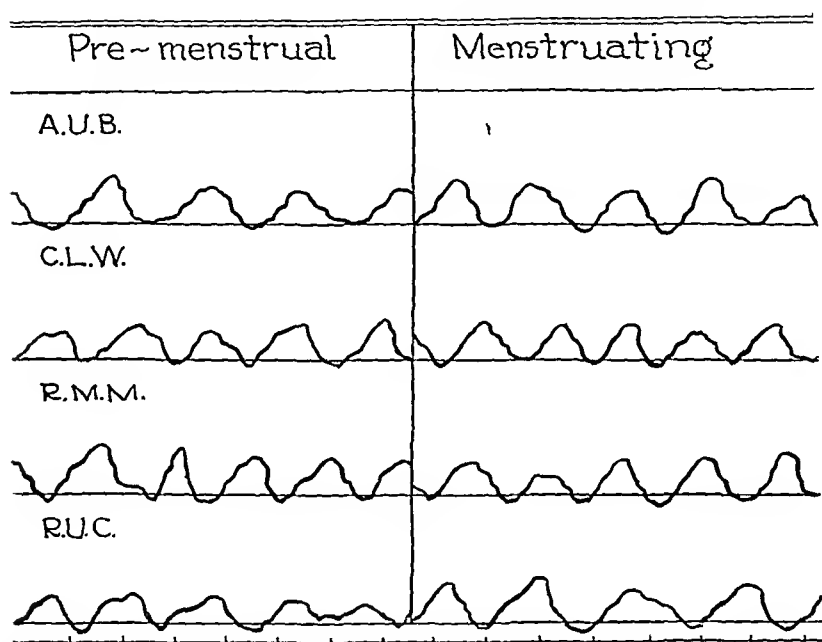


Fig. 2.—The premenstrual contractions have a relatively high amplitude. Each contraction returns to the base line, showing the absence of tetany. The menstruating contractions are similar and painless.

Considerable experience has shown that the tracings give an accurate picture of uterine contractility for the time of the cycle at which they are taken. The results on the same case at different phases of the cycle, and also in different patients are comparable when the technical procedure is the same in all experiments. Furthermore, the intrinsic pattern of motility is always brought out and cannot be altered by variations in pressure. For this study, the pressure in the system was kept between 30 and 50 mm. of mercury, so that the tracings could be fairly compared.

### MOTILITY IN NONPAINFUL MENSTRUATION

A number of patients with normal, nonpainful menstruation have been studied. The pattern of uterine motility in these cases has been previously reported.<sup>1</sup> During the follicular phase (pre-ovulatory), the con-

TABLE IV. PARITY AS FACTOR IN RESIDUAL HYPERTENSION

	TOTAL	HYPERTENSION	PER CENT
Primipara at time of toxemia	113	30	26.5
Multipara at time of toxemia	111	74	66.5

When the cases are divided into parities regardless of age, it is found that the incidence of residual hypertension after toxemia with the first pregnancy is 26 per cent, while after multiparous pregnancies, the incidence is 66 per cent. It is obvious, of course, that the primiparous individual is usually in the younger age groups, so that the factors of age and parity operate inseparably. All the multiparous individuals are grouped together, as there seemed to be no appreciable differences for the various parities, and when subdivided, the individual groups were too small to be significant.

TABLE V. TYPE OF TOXEMIA

	NO.	HYPERTENSION	PER CENT
Mild pre-eclamptic	48	26	54
Severe pre-eclamptic	117	55	47
Chronic nephritis	4	4	100
Essential hypertension	5	5	100
Total nonconvulsive	174	90	51.7
Mild eclampsia	34	9	26
Severe eclampsia	16	5	31
Total convulsive	50	14	28

In Table V the re-examined patients are grouped on the basis of the type of toxemia which occurred. Except for the 9 instances of previously recognized nephritis and essential hypertension, the type of toxemia seems of no particular significance in regard to subsequent hypertension. There is no appreciable difference in the incidence following mild or severe pre-eclamptic toxemia, nor is there any significant difference in the incidence between mild and severe eclampsia. Hypertension occurs subsequent to a nonconvulsive toxemia almost twice as frequently as after a convulsive toxemia. Eclampsia, however, occurs most frequently in the younger age groups, and in primiparas, and has, of course, a higher death rate, so undoubtedly the factors of age, parity, and the higher death rate at the time of the acute illness account in some degree for the higher incidence of residual hypertension after a nonconvulsive toxemia. In general, the severity of the toxemia plays no appreciable part in the frequency of later hypertension, and is of no particular significance in attempting to prognosticate the occurrence of later hypertensive phenomena.

The relationship between the systolic blood pressure at the time of admission to the Hospital for the toxemia and the later hypertension is shown in Table VI. In general, the higher the systolic pressure at the time of the toxemia the greater are the chances of residual hypertension. Whereas with systolic pressures less than 180, about one-third are followed by hypertension, about one-half are followed by hypertension when the systolic pressure is between 180 and 220, and about three-fourths when the original pressure was between 220 and

pain, showed a marked degree of tetany with the usual high amplitude contractions superimposed upon it (Fig. 3). This must be the typical pattern of uterine motility in dysmenorrhea because it was present in 13 of the 15 cases studied. Tetany was never seen in the nonpainful menstrual contractions. Contractions are similar in both groups, except for the tetany in the latter. In this group, not a single contraction ever returned to the base line, while in the nonpainful group all contractions returned either to the base line or below it. For the two patients who experienced typical dysmenorrhea, but who had a normal atonic type of contraction, there is no satisfactory explanation.

### DRUGS IN DYSMENORRHEA (MENSTRUATING)

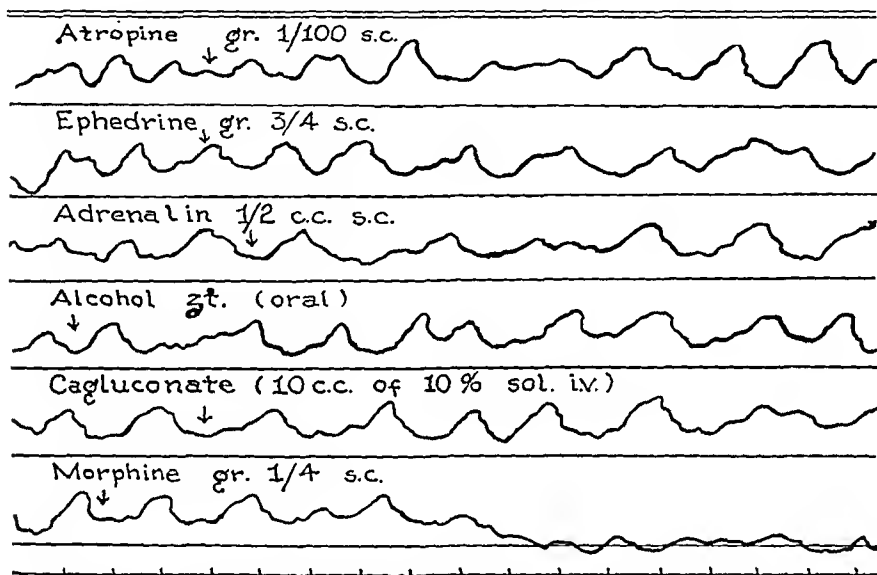


Fig. 4.—Atropine, ephedrine, adrenalin, alcohol, and calcium gluconate do not alter the contractions. Morphine abolishes tetany and diminishes the amplitude of each contraction.

#### EFFECT OF DRUGS ON MOTILITY IN PAINFUL MENSTRUATION

1. *Atropine*.—This drug has been frequently used on the theory that uterine cramps result from parasympathetic nerve stimulation. Atropine inhibits the parasympathetic nerve endings and thus should inhibit the contractions. Tracings were taken on three menstruating uteri after 1/100 gr. of atropine sulfate, subcutaneously had been given. No effect upon uterine motility could be demonstrated and there was no relief from pain (Fig. 4).

2. *Ephedrine*.—Two patients received ephedrine sulfate,  $\frac{3}{4}$  gr. t.i.d., for two days prior to the menses and on the first day of menstruation when the tracing was taken. Contractions were not altered in amplitude or frequency, nor was there any diminution of tetany. Pain was not relieved (Fig. 4).

3. *Adrenalin*.—On the assumption that sympathicomimetic drugs inhibit uterine contractions, the use of adrenalin has been advocated in dysmenorrhea. The effect of  $\frac{1}{2}$  c.c. (1-1000) subcutaneously in four patients was studied. Some diminution in tetany was observed, the

amplitude of contractions continued to be high, but did not return to the base line. Pain was not relieved (Fig. 4).

4. *Morphine*.—It is well known that morphine relieves the pain of dysmenorrhea. To determine whether this was only an effect upon the central nervous system, or whether it actually inhibited uterine contractions,  $\frac{1}{4}$  gr. of morphine was given subcutaneously to four patients. Within ten minutes the amplitude and rate of contractions were diminished, tetany abolished, and pain relieved (Fig. 4).

5. *Alcohol*.—Whiskey is a time-honored remedy for menstrual cramps. Two ounces of whiskey were given to each of three patients, all of whom said their pain was much relieved within thirty minutes. Traeings taken after thirty minutes showed no effect upon amplitude, rate, or tetany. Perhaps the vasodilating effect of alcohol may improve the relative isehemia of the myometrium (Fig. 4).

## HORMONES IN DYSMENORRHEA

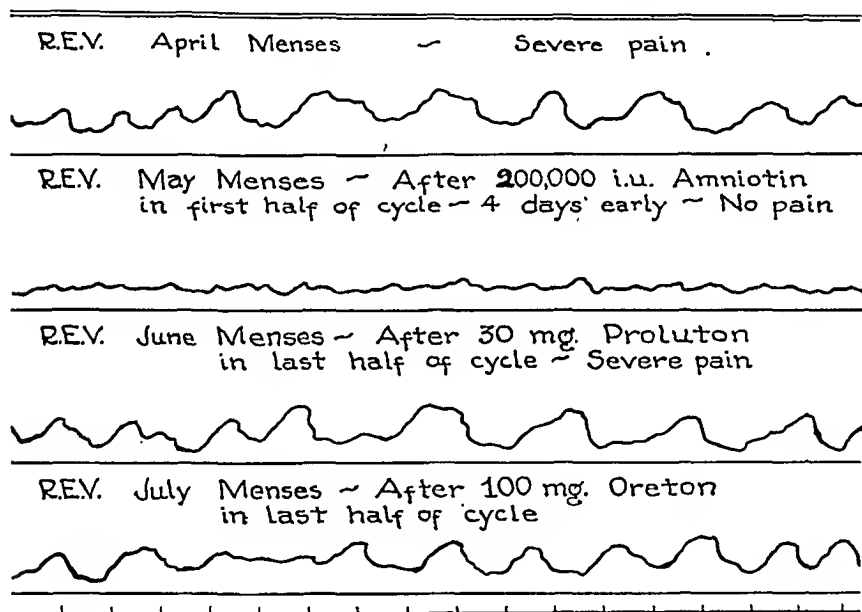


Fig. 5.—Estrogen in the form of amniotin prevented ovulation, and the menstrual contractions are low in amplitude because progesterone is absent. Progesterone in the form of proluton and testosterone in the form of oreton do not affect the pattern of uterine contractions.

6. *Calcium Gluconate*.—Ten cubic centimeters of 10 per cent solution of calcium gluconate were injected intravenously into one patient. There was no effect upon amplitude, rate, or tetany, and no relief from pain (Fig. 4).

### EFFECT OF HORMONES ON MOTILITY IN PAINFUL MENSTRUATION

1. *Estrogen*.—It has been observed by other investigators and confirmed by this study that dysmenorrhea occurs only with the high amplitude contractions of progesterone influence. Painful menstruation does not occur in the anovulatory cycle. Large amounts of estrogen given during the first half of the cycle inhibit the gonadotropic hormone of the anterior pituitary to the point where follicle rupture and luteiniza-

tion are prevented. In those cases where ovulation is not prevented, the luteinizing gonadotropin may be inhibited to the point where progesterone influence will be minimized and uterine contractions will have a lower amplitude. Two patients were each given 200,000 I.U. of estrogen (amniotin) in the follicular phase of the cycle. Ovulation did not occur as evidenced by the persistent proliferative endometrium, and the tracings during menstruation showed the low amplitude, high frequency type characteristic of estrogen dominance. In the absence of high amplitude contractions, no pain was experienced (Fig. 5).

2. *Progesterone*.—Since Reynolds reported the inhibitory action of progesterone on the myometrium, this hormone has appeared to provide logical therapy for dysmenorrhea.<sup>2</sup> It has already been shown, however, that this hormone is responsible for the high amplitude contractions which are always present in the luteal phase of the cycle. In nonpainful menstruation, progesterone also abolishes the tetany caused by estrogen. This tetany recurs in the dysmenorrheic tracings and the logical therapy, therefore, would seem to be the artificial administration of the hormone. Two patients each received 30 mg. of synthetic progesterone in the latter half of their cycle. High amplitude contractions persisted, there was no diminution of tetany, and no relief from pain. This observation increases our confusion regarding hormone therapy in general. I do not know why progesterone will inhibit uterine motility in vitro and apparently increases the force of uterine contractions in vivo. Why does progesterone abolish tetany in vitro, but in relatively large doses apparently does not affect it in vivo? Our increasing knowledge of the metabolism of progesterone may soon explain this apparent inconsistency (Fig. 5).

3. *Testosterone*.—This hormone is said to have a direct inhibitory influence upon the myometrium. One hundred milligrams of testosterone propionate were given to one patient during the latter half of her cycle. The tracing shows no effect upon the amplitude, rate, or tetany. Pain was not relieved (Fig. 5).

#### COMMENT

Rational therapy for dysmenorrhea must be directed toward the pathologic physiology of the uterine contractions. To say that the pain is psychogenic, or that certain individuals have a low threshold adds nothing to our knowledge of the condition. Furthermore, it is true that the contractions during painful menstruation have a tetany not present in the normal group. Wilson and Kurzrok have recently reported a similar study in which they conclude that the uterine contractions in dysmenorrhea are not different from those seen in the normally menstruating uterus.<sup>2</sup> With this conclusion I cannot concur. In 13 of my 15 patients, a marked degree of tetany was observed with superimposed high amplitude contractions. In the nonpainful menstruating uterus, the high amplitude, luteal type of contractions is always seen, but never associated with tetany. The question which will immediately come to the mind of an investigator in this field is how one can determine the base line from which to measure the degree of tetany. Most uteri become spastic upon introduction of the balloon, but this artificially induced tetany relaxes after several minutes. All of the tracings in this study

were done at least fifteen minutes after the introduction of the balloon. In all cases morphine, gr.  $\frac{1}{4}$ , was given at the end of the experiment, fifteen minutes allowed to elapse, and the tracing again taken. This was done in order to establish the base line for each uterus. In the 7 cases of nonpainful menstruation, the relaxing effect of morphine did not greatly alter the base line to which each contraction returned. However, in the dysmenorrheic uteri the writing point dropped from  $\frac{1}{2}$  to  $1\frac{1}{2}$  cm. below the lowest point of uterine contraction after giving  $\frac{1}{4}$  gr. of morphine (Fig. 4). This demonstrates rather conclusively that the dysmenorrheic uterus is a tetanic uterus.

#### SUMMARY

1. Dysmenorrhea occurs in the presence of high amplitude contractions superimposed upon tetany.

2. High amplitude contractions occur only in the presence of a corpus luteum. It follows therefore, that dysmenorrhea occurs only in the ovulatory cycle.

3. Atropine, ephedrine, adrenalin, and calcium gluconate do not alter uterine motility in dysmenorrhea and give no pain relief.

4. Alcohol does not alter uterine motility, but appears to diminish the pain through its effect either upon the nervous system or by its vasodilating effect upon the arterioles of the myometrium.

5. Morphine diminishes the amplitude of the contractions, abolishes tetany, and relieves the pain.

6. Estrogen in the first half of the cycle in large doses may either prevent ovulation or inhibit the luteinizing hormone of the anterior pituitary, thereby curtailing the progesterone effect on the uterus. Since high amplitude contractions occur only with progesterone, these are eliminated and pain relieved.

7. Progesterone administered subcutaneously does not change the contractions during menstruation in the ovulatory cycle and gives no pain relief.

8. Testosterone has no effect upon the menstrual contractions in the ovulatory cycle and gives no pain relief.

#### REFERENCES

- (1) *Wilson, L., and Kurzrok, R.*: *Endocrinology* 27: 23, 1940. (2) *Novak, E., and Reynolds, S. R. M.*: *J. A. M. A.* 99: 1466, 1932. (3) *Moir, C.*: *Tr. Edinburgh Obst. Soc.*, p. 93, 1934.

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Rau, R. K., Aiyar, A. A., and Mathew, T. V.: *Quintuplets. A Record of a Premature Delivery*, *Brit. M. J.* 1: 127, 1940.

A case of monozygotic quintuplets is reported. The fetuses were expelled during the sixth month of gestation and were attached by five separate umbilical cords to a single placenta which revealed one chorion and five amniotic sacs.

The infants, which averaged 14.0 cm. crown-rump length, died a few minutes after birth.

FRED L. ADAIR AND RAY YOUNG

## POSTABORTAL TETANUS

A REVIEW OF THE LITERATURE, AND A REPORT OF 14 ADDITIONAL CASES

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POSTABORTAL tetanus as an entity has been well established by the work of Chantemesse and Widal,<sup>1</sup> Heyse,<sup>2</sup> Rubeska,<sup>3</sup> and others,<sup>4, 5, 43, 45</sup> who were able to isolate the causative organism from uterine discharges. It is of infrequent occurrence and has occasioned but minor notice in even such an excellent work as Taussig.<sup>42</sup>

In 1898, at the Congress of Gynecology and Obstetrics at Marseilles, Sepet<sup>5</sup> reported 125 cases of puerperal tetanus (48 postabortal). Schneider<sup>4</sup> was able to collect only 109 cases from the literature, to which he added two of his own (1925). While those who refer to the previous literature at all, cite Schneider's series, there are scant references to Sepet's splendid report. Schneider's survey focused attention upon postabortal tetanus, and his paper was followed by the reports of Auvray,<sup>6</sup> Houel, Lesini and Morand,<sup>7</sup> Chalier and Rousset,<sup>8</sup> Byrne,<sup>9</sup> Hebold,<sup>10</sup> Mattson and Starkey,<sup>11</sup> Laffont, Ezes, and Mereaur,<sup>12</sup> Martinez,<sup>13</sup> Arnaudet,<sup>14</sup> Sicard,<sup>15</sup> Duvoir and associates,<sup>16</sup> Valenti,<sup>17</sup> Janbon and associates,<sup>18</sup> Bernardbeig,<sup>19</sup> Warembourg and associates,<sup>20</sup> Kernbach and Dachnovici,<sup>21</sup> de Rougemont and Clavel,<sup>22</sup> Rossi,<sup>23</sup> and Petersen.<sup>24</sup> More recently cases have been reported by Komaromy,<sup>25</sup> Harteman,<sup>26</sup> Desbonnets,<sup>27</sup> Breborowicz,<sup>28</sup> Blondin,<sup>29</sup> Turries and associates,<sup>30</sup> Ferron and Torlet,<sup>31</sup> Menendez,<sup>32</sup> Ximeno,<sup>33</sup> de Barros,<sup>34</sup> Goyer and Bernard,<sup>35</sup> and Goyer<sup>36</sup> and more recently that of Bush<sup>37</sup> (see Table I). It is interesting to note that of these only four reports<sup>9, 11, 25, 37</sup> have appeared in English. The majority of the reports have originated on the continent, and are chiefly French and German. One notes with interest that no collected series has appeared from India, where Knight<sup>38</sup> has indicated conditions for the occurrence of post-partum tetanus would seem to be ideal.

We became interested in postabortal tetanus by the recent occurrence in and recovery of a patient (Case 6) on the Tulane Gynecological Service at Charity Hospital and were able to collect 13 additional cases from the services at Touro Infirmary and Charity Hospital. We feel that such a large local series tends to show that the condition is probably more common than the literature indicates.

### CASE REPORTS

CASE 1.—C. H. (No. S363), married, negress, 22 years of age, was admitted to the emergency room on Mar. 14, 1926 at 4:50 P.M., in convulsions. A history of criminal abortion ten days previously, and physical



TABLE I

AUTHOR	NO. OF CASES	NO. RECOVERED	MORTALITY %
Schneider <sup>4</sup>	111	10	91
Auvray <sup>6</sup>	2	2	100
Houel and others <sup>7</sup>	2	0	100
Chalier and Rousset <sup>8</sup>	1	0	100
Byrne <sup>9</sup>	1	0	100
Hebold <sup>10</sup>	1	0	100
Mattson and Starkey <sup>11</sup>	1	1	0
Laffont and others <sup>12</sup>	1	0	100
Martinez <sup>13</sup>	1	1	0
Arnaudet <sup>14</sup>	1	0	100
Sicard <sup>15</sup>	2	1	50
Duvoir and others <sup>16</sup>	1	0	100
Valenti <sup>17</sup>	1	1	0
Janbon and others <sup>18</sup>	1	0	100
Bernardbeig <sup>19</sup>	1	0	100
Warembourg <sup>20</sup>	1	0	100
Kernbach and Dachnovici <sup>21</sup>	2	0	100
Rougemont and Clavel <sup>22</sup>	1	0	100
Rossi <sup>23</sup>	1	1	0
Petersen <sup>24</sup>	1	0	100
Komaromy <sup>25</sup>	1	0	100
Hartman <sup>26</sup>	1	0	100
Desbonnets <sup>27</sup>	1	0	100
Breborowicz <sup>28</sup>	2	0	100
Blondin <sup>29</sup>	2	0	100
Turries and others <sup>30</sup>	1	1	0
Ferron and Torlet <sup>31</sup>	1	0	100
Menendez <sup>32</sup>	1	0	100
Ximeno <sup>33</sup>	3	2	33
de Barros <sup>34</sup>	1	0	100
Goyer and Bernard <sup>35</sup>	2	1	50
Goyer <sup>36</sup>	1	1	0
Bush <sup>37</sup>	5	0	100
This series	14	6	57
Collected literature			
Total cases	170	28	84

findings compatible with tetanus were obtained. A diagnosis of tetanus was made in the admitting room. Patient died fifteen minutes after admission. 20,000 units antitetanic serum, intramuscularly, and 20,000 units intravenously were administered by the admitting physician. Sodium bromide and chloral hydrate were used for sedation. Autopsy was performed by the coroner.

CASE 2.—C. H. (No. G12005), married, negress, 34 years, was admitted on May 16, 1929, at 11:10 P.M., with a history of an abortion eight days prior to admission. On admission she had an elevated temperature, rigid neck, and the abdominal musculature was tense. Spinal fluid pressure was normal. Examination of fluid presented no unusual findings. She received a total of 70,000 units of antitetanic serum intramuscularly, and 30,000 units of antitetanic serum intravenously. Sedations of morphine and chloralone were used. The patient seemed to improve markedly, her maximum temperature of 105° F. on the second day returned to normal by the third day. On the fifth day she developed pneumonia which continued progressively worse, and she died on the eleventh hospital day. Autopsy was performed by the coroner.

CASE 3.—C. H. (No. S455), married, negress, 22 years of age, was admitted on Sept. 6, 1931, eight days after having sustained a criminal abortion. She was admitted with a chief complaint of difficulty in eating and slight convulsions on stimulation. Day after admission her temperature rose to 102.2° F. and therefore gradually declined to normal. She received 40,000 units antitetanic serum intramuscularly on admission. During the next four days she received an additional total dose of 120,000 units of antitetanic serum intramuscularly. Chloral hydrate, sodium amytal, and chloratone were employed for sedation. Nutrition was maintained by tube feeding. She made an uneventful recovery and was discharged Oct. 1, 1931.

CASE 4.—C. H. (No. 774 S 461), unmarried negro school teacher, 23 years of age, gravida i, last menstrual period two months previously, had an abortion nine days before entering the hospital on Jan. 7, 1932 at 9:05 P.M. On admission she was unable to open the mouth, and had rigidity of neck muscles. Spinal fluid pressure was slightly increased. Other laboratory findings were negative. She was immediately given 7,500 units of antitetanic serum intraspinaly. She received a total dosage of 5,500 units of antitetanic serum intramuscularly and 29,000 units intravenously. Sodium amytal and morphine were used as sedation. Nutrition was maintained by infusions and Levin tube feeding. Her temperature rose progressively to 105° F., pulse 136, respiration 34. She died on Jan. 10, 1932, at 9:55 A.M. At autopsy, necrotic placental rests were found in the uterine cornu. She also had a terminal bilateral bronchopneumonia.

CASE 5.—C. H. (No. H38649 S 477), married, negress, 29 years of age, gravida vii, was admitted on Oct. 22, 1932, at 7:15 P.M. She gave a history of a spontaneous abortion eight days earlier at or about the seventh week of gestation. The chief complaint on admission was difficulty in swallowing. Laboratory findings were negative. She received a total dosage of 40,000 units of antitetanic serum intramuscularly, and 20,000 units intravenously. Chloral hydrate, bromides, avertin, and morphine were used as sedatives. She grew progressively worse, temperature gradually rose to a maximum of 106° F. just prior to death, which occurred on Oct. 28, 1932, at 7:30 A.M. Coroner performed autopsy with a report of tetanus and postabortal septicemia.

CASE 6.—A. G. (T No. L1256), married, white multigravida, was admitted on Mar. 2, 1934, with a history of a criminal abortion by a local midwife twelve days previously. She manifested her symptoms for the first time two days prior to admission. On admission she had an elevated temperature and trismus. Laboratory findings were negative. She received 30,000 units of antitetanic serum intrathecally and 30,000 units intravenously. Sodium amytal was used for sedation. Her nutrition was maintained by Levin tube. Due to hemorrhage a dilatation and curettage were done and a large quantity of infected products of pregnancy removed. Patient was discharged on Mar. 11, 1934, symptom free.

CASE 7.—Mrs. W. P. (T No. L6317), 17-year-old gravida iv, was admitted Oct. 5, 1934, with complaints of pain in the back and neck, trismus, and uterine bleeding. She gave a history of two criminal abortions, one two years ago, and the last ten days previous to admission.

Her symptoms began three days prior to admission. Laboratory reports were essentially negative except for a marked leucocytosis. She received a total of 110,000 units of antitetanic serum intravenously and 245 gr. of sodium amytal in dosages of  $7\frac{1}{2}$  gr. over a period of twenty days. Sedation was then maintained with bromides and chloral hydrate for a period of three days. She was discharged symptom free, Nov. 7, 1934.

CASE 8.—Mrs. M. M. (T., No. L7839), aged 21 years, housewife, was admitted Dec. 13, 1934, 1:40 P.M. with opisthotonus and trismus. Patient had a criminal abortion seven days before admission. She developed convulsions on the fifteenth and was given sodium amytal. This was repeated on the sixteenth and patient died at 8:55 P.M. She had also received chloral hydrate and sodium amytal in an attempt to control convulsions. Her temperature had mounted steadily from the admission temperature of 98° F. to a terminal temperature of 106.6° F.

CASE 9.—Mrs. S. M. N. (T., No. 38-72935, C. H.), white oetigravida, aged 31 years, was admitted to the Gynecological service Sept. 10, 1938, presenting a history of an induced abortion fourteen days previously, and exhibiting the signs of tetanus; viz., risus sardonius, stiff neck, increased biceps, and patellar reflexes. Muscular pains had begun one week prior to admission, growing progressively worse. Patient's husband was employed as a riding club instructor; and the patient stated that she had spent considerable time around horses. Her physician had given her 3,000 units of antitetanic serum intramuscularly. The cervical canal was dilated about 2 cm. The uterine discharge was foul. The conjunctival and intradermal tests for tetanus antitoxin proved negative; consequently, 50,000 units were administered intravenously. The cerebrospinal fluid pressure was found to be 10 mm. Hg, rising to 18 mm. as the result of application of pressure to the neck veins, and falling promptly to the original figure when the pressure was released. The fluid was crystal clear, and proved to be "negative" upon microscopic, chemical and cultural study. Twenty-seven cubic centimeters were permitted to escape drop by drop. An equivalent quantity of tetanus antitoxin (Gilliland, 80,000 American units) was introduced. During the subsequent days, a total of 280,000 units were administered. Of this amount 200,000 units were given intravenously.

Oral temperature was 102° F., with pulse rate of 100, respiratory rate of 25 at time of admittance. Maximum temperature was 102.2° F. (axilla) on the third hospital day. At that time pulse was 130 per minute; patient was afebrile after the sixth day. Nutrition was maintained by Levin tube feedings. Total of 41.25 gr. of sodium amytal were given intramuscularly. Patient was discharged Sept. 29, 1938.

CASE 10.—H. T. (C. H., No. 38-67750), 24-year-old, colored, gravida vi, complaining of "jerking in throat started by noise" and mild convulsive seizures on the day of admission. Patient had an abortion four days previously. She received 40,000 units antitetanic serum intramuscularly and 40,000 units intravenously. She was also given avertin. Nutrition was administered by Levin tube and infusions. She died on Sept. 27, 1938, at 5:18 P.M. Coroner reported postabortal tetanus.

CASE 11.—A. P. (C. H., No. 138-76076), 20-year-old unmarried negress, gravida i, was admitted to the hospital on Nov. 20, 1938. She stated that she had had "lockjaw for three days." Criminal abortion was

performed seven days previously. Laboratory findings were negative. She received 20,000 units of antitetanic serum intravenously, and 40,000 units intramuscularly; also avertin and sodium phenobarbital. Nutrition was given by infusion and Levin tube. She died Nov. 24, 1938. Coroner's report: postabortal tetanus.

CASE 12.—Mrs. E. B. (T., No. S 2784), 35 years, gravida ii, was admitted Mar. 26, 1940, with trismus and rigidity of neck. Patient gave a history of an abortion six days earlier and stated that the vagina had been packed by a midwife the day prior to admission. She received 160,000 units of antitetanic serum intravenously and 160,000 units intramuscularly. On March 27 she was given 120 gr. of sulfanilamide which was followed by cyanosis. She was also given seconal and morphine. Nutrition was given by infusion and stomach tube. Patient recovered uneventfully and was discharged on April 18, 1940.

CASE 13.—Mrs. S. R. (T., No. S 6838), 26 years, gravida i, was admitted with profuse uterine bleeding which she stated was an excessive flow but at her normal period. Two days after admission she had a convulsion after swallowing. A history was later obtained of eriminal abortion fourteen days previous to admission. She received 80,000 units of antitetanus serum intravenously, and chloratone as a sedative. She developed a "trigger zone" in the pharynx and had a mild convulsion whenever she attempted to swallow. Her condition continued steadily worse, and she died Aug. 3, 1940, at 12:25 P.M. Autopsy was performed. Diagnosis: postabortal tetanus.

CASE 14.—Miss K. K. S. (T., No. S 4411), was admitted May 9, 1940, with bleeding and a history of eriminal abortion performed the previous day. Laboratory findings were negative. She was afebrile and getting along very well until seven days after admission when she developed the classical signs of tetanus. She was given 80,000 units of antitetanus serum, intramuscularly and 40,000 units intravenously, 120 gr. of sulfanilamide, 30 c.c. of neoprontosil, a transfusion, morphine and sodium phenobarbital. She recovered and was discharged May 26, 1940.

#### DISCUSSION

Tetanus occurs more frequently after abortion than after full-term delivery. It occurs much more frequently after eriminal than after spontaneous abortion. In this series, there was but one spontaneous abortion. The onset of symptoms occurs between the sixth and twelfth postabortal day, though occasionally symptoms have been reported earlier, in rare instances occurring immediately after the termination of pregnancy. Auvray and Frantz<sup>43</sup> state that the incubation period is much shorter, ranging between one and six days. In this series the earliest onset of symptoms was four days after abortion and the latest sixteen days (see Table II).

As DeLee<sup>41</sup> points out, "the pathology, symptoms, diagnosis and treatment do not differ from that of surgical tetanus." Often, in fact usually, the symptoms are those of classical tetanus. However, they are not infrequently atypical. There are instances reported where the only sign was a slight rigidity of the abdominal muscles, to be followed much later by the other signs of tetanus. Only three of our patients

TABLE II

CASE	RACE	AGE	GRAVIDA	INCUBA- TION PERIOD DAYS	TREATMENT*	OUTCOME
1	Colored	22	?	10	A.T.S. 20,000 units I.V. 20,000 units I.M. Sodium bromide Chloral hydrate	Died
2	Colored	34	?	8	A.T.S. 70,000 units I.M. 30,000 units I.V. Morphine Chloratone	Died
3	Colored	22	?	8	A.T.S. 160,000 units I.M. Chloral hydrate Sodium amytal	Recovered
4	Colored	23	i	9	A.T.S. 7,500 units intra- thecally 5,500 units I.V. 29,000 units I.M. Sodium amytal Morphine	Died
5	Colored	29	vii	8	A.T.S. 40,000 units I.M. 20,000 units I.V. Chloral hydrate Bromide Avertin Morphine	Died
6	White	28	?	10	A.T.S. 30,000 units I.V. 30,000 units intra- thecally Sodium amytal	Recovered
7	White	17	iv	10	A.T.S. 110,000 units I.V. Sodium amytal Bromides Chloral hydrate	Recovered
8	White	21	i	7	Chloral hydrate Sodium amytal	Died
9	White	31	viii	7	A.T.S. 250,000 units I.V. 160,000 units intra- thecally Sodium amytal	Recovered
10	Colored	24	vi	4	A.T.S. 40,000 units I.M. 40,000 units I.V. Avertin	Died
11	Colored	20	i	7	A.T.S. 20,000 units I.V. 40,000 units I.M. Avertin Phenobarbital	Died

\*A.T.S., Antitetanus serum; I.V., intravenously; I.M., intramuscularly.

TABLE VI. SYSTOLIC BLOOD PRESSURE AT TIME OF TOXEMIA ADMISSION

SYSTOLIC	NO. PATIENTS	NO. SUBSEQUENT HYPERTENSION	PER CENT
240	9	9	100
220	7	5	71
200	18	9	50
180	49	25	51
160	93	28	30
140	48	16	33

240, while it occurred in all of those in whom the original reading was 240 or more. While the results are not entirely conclusive, in general it may be surmised that the higher the systolic blood pressure at the time of the toxemia, particularly above 200 mm., the greater the possibility of persistent high blood pressure.

TABLE VII. DIASTOLIC BLOOD PRESSURE ADMISSION

DIASTOLIC	NO. PATIENTS	NO. HYPERTENSION	PER CENT
180	1	1	100
160	9	7	77
140	17	10	58
120	71	31	44
100	117	47	40
90	9	5	55

The cases are analyzed in Table VII on the basis of the diastolic blood pressure at the time of admission for the toxemia, and the figures do not reveal any very conclusive relationship, unless the diastolic pressure was at a very high level. When the diastolic pressure was above 160 mm., at least three-fourths of the patients had subsequent hypertension, while the incidence was about the same for the various levels below 160. However, the number of cases in the higher levels are so few that the results are probably not significant.

TABLE VIII. EFFECT OF SUBSEQUENT PREGNANCIES

PREG. SINCE	NO. PATIENTS	HYPERTENSION	PER CENT	NO. REPEAT TOXEMIA
<i>Nonconvulsive</i>				
0	34	6	17	--
1	19	5	26	9
2	10	3	30	7
3	5	2	40	2
4	5	3	60	3
5	3	2	66	2
<i>Convulsive</i>				
0	18	3	16	--
1 to 4	19	6	32	--

Of the 224 patients re-examined, 113 of them were primiparas at the time of their toxemia, 37 of whom had eclampsia. In Table VIII, we attempt to analyze these cases in relation to the effects of subsequent pregnancies. The table shows, without consideration of the age factor, that in individuals with toxemia during their first pregnancy, but who at the time of the follow-up examination had had no other pregnancies, the incidence of hypertension was 16 per cent after eclampsia, and 17 per cent after toxemia without convulsions. On the other hand when subsequent pregnancies occurred, the incidence of hypertension was prac-

administration of antitetanic serum would seem to be of definite value. More recently, the experimental work of Shumacker, Firor and Lamont<sup>57</sup> and of Firor<sup>51</sup> has tended to confirm the superior value of intrathecally administered antitetanic serum over its administration via the other routes. However, Deitrich<sup>52</sup> has reported the death of children following the use of intrathecally administered antitetanic serum, the clinical picture resembling bulbar poliomyelitis, or some other disease with medullary pressure or edema.

We have had little experience with the use of intrathecally administered antitetanic serum. Of the 3 patients in this series who received serum via that route, two recovered. When a patient, who has developed tetanus after a very short incubation period, and/or presents marked signs of tetanus, presents herself, it would seem to be advisable to use the serum by the intrathecal route.

The following routine may be adopted for treatment of postabortal tetanus:

1. The patient should be placed in a quiet room, shielded from noises and external stimuli. She should be given sodium amytal, gr.  $7\frac{1}{2}$ , either orally or intravenously, depending upon the severity of the symptoms. This should be repeated at sufficiently frequent intervals to maintain the patient in a narcotized state until all danger of spasms has passed. The patient should be tested for sensitization to antitetanic serum.

2. Antitetanic serum should be administered: 50,000 units intramuscularly, 50,000 intravenously. If the incubation period has been short, or if the symptoms are severe, intrathecal administration of 50,000 units of antitetanus serum may be added to this routine. 30,000 units antitetanus serum should be given intramuscularly and intravenously on each of the next three days. Additional dosages of serum, or larger quantities may be given depending upon the clinical picture.

3. Nutrition should be maintained by tube feeding and/or by intravenous drip.

4. The bladder and bowel function of the patient should be watched. When necessary the nasopharynx should be frequently aspirated, and the patient, if narcotized for a long period, should have frequent changes of position.

The treatment of the site of injury was shown to be of importance long ago. Thus Cummins<sup>45</sup> was able to report a series in which a mortality of 64.4 per cent was reduced to 51.5 per cent by the use of excision of the wound and complete débridement.

With this fact in mind there has been much discussion in the literature as to the usefulness of hysterectomy as an adjunct to the aforementioned routine of therapy in postabortal tetanus. Its advocates unfortunately have been unable to demonstrate any improvement in the mortality rate of their series. Hysterectomy is certainly of questionable value. One cannot insist that it has increased the mortality or decreased the chance of survival in the particular patient. One cannot argue that, because a patient who has sustained a hysterectomy has

TABLE II—CONT'D

CASE	RACE	AGE	GRAVIDA	INCUBATION PERIOD DAYS	TREATMENT*	OUTCOME
12	White	35	ii	6	A.T.S. 160,000 units I.V. 160,000 units I.M. Sulfanilamide Seconal Morphine	Recovered
13	White	26	i	16	A.T.S. 80,000 units I.V. Chloratone	Died
14	White	24	i	8	A.T.S. 80,000 units I.M. 40,000 units I.V. Sulfanilamide Neoprotosil Transfusions Morphine	Recovered

were admitted with actual "lockjaw." Since postabortal tetanus may develop para passu with puerperal septicemia or other complications, its symptomatology may be masked. This finding has repeatedly been reported.

All are agreed that adequate therapy is based on the following factors: (1) sedation, (2) adequate use of antitetanic serum, and (3) maintenance of nutrition. The combination of serum and sedation is important. Thus in Cooper's<sup>46</sup> series the mortality of 59.4 per cent when sedation was used alone was reduced to 29.3 per cent when sedation and serum were used. The type of sedation varies widely, the barbiturates being in greatest use. Sodium amytal, avertin,<sup>56</sup> chloral hydrate, and many other drugs have had their warm advocates. We feel that satisfactory results are obtained by the use of sodium amytal in doses of 7½ gr. repeated as often as required for narcosis.

So little is known about the amount of toxin liberated, and the host resistance in any given instance, that we feel that large amounts of antitetanic serum are necessary in the treatment of the individual case. There has been considerable discussion in the literature as to the route of administration of the serum. Recently, the intrathecal route has been added to the intravenous, intramuscular, and subcutaneous routes, and widely advocated.

Much literature has grown up about the question of intrathecally administered serum, and clinicians have differed as to its effectiveness. Gage and DeBailey,<sup>47</sup> Wainwright<sup>48</sup> and others do not advise its use. Golla<sup>49</sup> and Calvin and Goldberg<sup>50</sup> are dubious as to its value. Bates<sup>55</sup> uses a total of 40,000 units subcutaneously, or intravenously, and 7,500 units intrathecally as the initial dose. Vener,<sup>53</sup> whose mortality rate of 29 per cent in 100 cases of tetanus is perhaps the lowest reported, routinely gives 200,000 units of antitetanic serum, 40,000 units being given intracranially. Yodanis<sup>54</sup> uses the latter route and reports a mortality of 50.6 per cent in 443 cases. From these reports the intrathecal



## SUMMARY

1. Fourteen cases of postabortal tetanus are reported, with a mortality of 57 per cent.

2. The literature of postabortal tetanus has been surveyed and note is made of the paucity of American and English reports, and of the high mortality (90 per cent) which still persists.

3. We feel that this series should help to focus attention on the syndrome and stimulate further reports, and provoke a more careful watch for symptoms of tetanus in cases of criminal abortion.

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## REFERENCES

- (1) *Chantemesse and Vidal*: Bull. méd., Paris 74: 1, 1889. (2) *Heise*: Deutsche med. Wehnscr. 14: 318, 1893. (3) *Rubenska*: Arch. f. Gynäk. 54: 1, 1897; 58: 177, 1899. (4) *Schneider, G. H.*: Klin. Wehnscr. 4: 2438, 1925. (5) *Sepet*: Congrès de Gynécologie et d'obstetrique, Marseilles, 1898. (6) *Auvray*: Bull. Acad. de méd., Paris 96: 58, 1926. (7) *Houel, Lesini, and Morand*: Bull. Soc. d'obst. et de gynéc. 17: 361, 1928. (8) *Chalier, J., and Rousset, J.*: Lyon méd. 141: 645, 1928. (9) *Byrne, L. H. H.*: China M. J. 42: 526, 1928. (10) *Hebold, O. H.*: Zentralbl. f. Gynäk. 52: 2661, 1928. (11) *Mattson, C. H., and Starkey, T. A.*: Minnesota Med. 14: 737, 1931. (12) *Laffont, Ezès, and Mereaur*: Bull. Soc. d'obst. et de gynéc. 21: 542, 1932. (13) *Martinez, U.*: Clinica 9: 97, 1932. (14) *Arnaudet, A.*: Rev. gén. de clin. et de thérap. 46: 631, 1932. (15) *Sieard, A.*: Bull. méd., Paris 46: 897, 1932. (16) *Duvoir, M., Pollet, L., and Conder, R.*: Bull. et mém. Soc. méd. d. hôp. de Paris 49: 1160, 1933. (17) *Valenti, S.*: Bull. d. Soc. piemontese di ostet. e ginec. 1: 411, 1933. (18) *Janbon, Ratie, and Vedel*: Arch. Soc. d. sc. méd. et biol. de Montpellier 15: 332, 1934. (19) *Bernardbeig*: Bull. Soc. d'obst. et de gynéc. 24: 359, 1935. (20) *Warembourg, Decoulx, H., Bedrine, and Bastien*: Echo méd. du Nord. 4: 44, 1935. (21) *Kernbach, M., and Dachnowicz, V.*: România med. 13: 121, 1935. (22) *de Rougemont and Mme. Clavel*: Lyon chir. 32: 445, 1935. (23) *Rossi, A.*: Monde méd. Paris 46: 53, 1936. (24) *Petersen, E.*: Acta obst. et gynec. Scandinav. 17: 36, 1937. (25) *Komaromy, G. G.*: Am. J. OBST. & GYNEC. 34: 687, 1937. (26) *Harteman, J.*: Bull. Soc. d'obst. et de gynéc. 26: 747, 1937. (27) *Desbonnets, G.*: J. de chir. 53: 49, 1939. (28) *Breborowicz, H.*: Nowiny lek. 50: 635, 1938. (29) *Blondin, S.*: Medicine 19: 273, 1938. (30) *Turries, Chosson, J., and Sansot*: Bull. Soc. gynéc. et d'obst. 28: 91, 1939. (31) *Ferron, E., and Torlet, J.*: Mém. Acad. de chir. 65: 1031, 1939. (32) *Menendez, O.*: Rev. cubana de obst. y ginec. 1: 89, 1939. (33) *Ximeno, M.*: Arch. urug. de med., cir. y especialid. 16: 449, 1940. (34) *de Barros, O. M.*: Rev. clin. de São Paulo 7: 119, 1940. (35) *Goyer, R., and Bernard, J.*: Arch. méd. d'Angers 44: 83, 1940. (36) *Goyer, Robert*: Mém. Acad. de chir. 65: 172, 1939. (37) *Bush, W. L.*: J. A. M. A. 116: 2750, 1941. (38) *Knight, H. W.*: New Orleans M. & S. J. 86: 172, 1933. (39) *Mondor*: Les Avortements Mortels, Paris, 1936. (40) *Vinay*: Arch. de tocol. et de gynéc. Paris 19: 179, 1892. (41) *DeLee, J. B.*: The Principles and Practice of Obstetrics, ed. 6, Philadelphia, 1933, W. B. Saunders Company. (42) *Taussig, F. J.*: Abortion Spontaneous and Induced, St. Louis 1936, The C. V. Mosby Co. (43) *Auvray and Frantz*: Gaz. d. hôp. July 21, 1926. (44) *Lapauze*: Le tetanos uterin abortif, Thèse de Medicine, Bordeaux, 1919. (45) *Cummins, S. L.*: Quoted by Jensen, West. J. Surg. 48: 146, 1940. (46) *Cooper, N. A.*: Lancet 2: 930, 1917. (47) *Gage, I. M., and DeBailey, M.*: South. Surgeon 4: 240, 1935. (48) *Wainwright, J. M.*: Arch. Surg. 12: 1062, 1926. (49) *Golla*: Lancet 2: 966, 1917. (50) *Calvin, J. K., and Goldberg, A. H.*: J. A. M. A. 94: 1977, 1930. (51) *Firor, W. M.*: Arch. Surg. 41: 299, 1940. (52) *Deitrich, H. F.*: Am. J. Dis. Child. 59: 693, 1940. (53) *Vener, H. L.*: California & West Med. 48: 3, 1938. (54) *Yodh*: Brit. M. J. 1: 855, 1937. (55) *Bates, C. O.*: Am. J. Surg. 18: 58, 1932. (56) *Boyce, F. F., and McFetridge, E. M.*: Internat. S. Digest 19: 131, 1935. (57) *Shumacker, H. B., Jr., Firor, W. M., and Lamont, A.*: Surgery 8: 1, 1940.

survived, the procedure was of value. Dilatation and curettage, or manual evacuation of the uterine contents has also been advocated by some authors, based on the principle that any tissue remaining in the uterus may contain the tetanus bacilli and spores, and so act to prolong the infection and increase its severity. However, postabortal dilatation and curettage are generally and correctly condemned.

With the same idea some authors advocate dilatation of the cervix followed by the insertion into the uterus of a large amount of antitetanic serum through a catheter. Others have advised the irrigation of the uterus with oxygen and Dakin's solution. These procedures were not used in any of the cases of our series. It is interesting to note that the patient in Case 6 in our series had a curettage which was done because of severe hemorrhage, and recovered. The prolonged incubation period in this patient (fourteen days), together with the use of intravenously and intrathecally administered serum, may account for the recovery of this patient.

The incidence of postabortal tetanus is a matter of some conjecture. In the fifteen-year period studied, Touro Infirmary had 6 cases so diagnosed out of a markedly smaller total admissions than Charity Hospital which, in the same period, had only 8 recorded cases of postabortal tetanus. The prognosis is poor. Vinay<sup>40</sup> reported a mortality of 89 per cent which corroborates the findings of Schneider who reported a mortality of 91 per cent and of Rubeska of 100 per cent. In Sepet's series the mortality was 86 per cent, while Auvray reporting on 41 cases (collected since Sepet's series) reported a mortality of 85.36 per cent.

In Mondor's<sup>39</sup> more recent series (1934) of 51 cases, the mortality was 76 per cent. It is interesting to note the very minor improvement in mortality in the reports which fall in the period during which antitetanus serum has been known and used and the reports which antedated the widespread use of antitetanus serum. In the collected literature, the mortality is approximately 85 per cent, while of the 14 cases herein reported there was a mortality of 57 per cent.

It is interesting to compare the mortality at the two institutions we have studied. At Charity Hospital two patients out of 8 recovered, a mortality of 75 per cent, while at Touro Infirmary 4 patients out of 6 recovered, a mortality of 33 per cent. While the mortality rate of Charity Hospital series is quite high it is not surprising considering the fact that patients usually present themselves for treatment later, due to the fact that many come from distant points, and due to the secrecy which surrounds the criminal procedure which they have sustained. It is this same secrecy which accounts for many more deaths from postabortal tetanus which occur in patients who probably never reach the hospital.

Although the proper emphasis has been placed upon the prevention of traumatic or surgical tetanus, there is an appalling lack of attention to the prevention of postabortal tetanus. We feel that it would be wise to administer a prophylactic dose of antitetanic serum to every woman who has submitted to a criminal abortion.

the vulva can reach the cervix by active migration through the entire length of the acid vagina. One of us (W. S.) had the opportunity to observe eight cases of normal pregnancies in women each with a perfectly intact hymen. In some of these cases the opening of the hymen measured only 3 to 4 mm. History confirmed by the anatomic findings gave evidence that in all of these cases the ejaculated semen had been deposited at the vulva outside of the diaphragm of the hymen. In all of these cases the spermatozoa had to pass the entire length of the acid vagina (but, possibly in some, a strong alkaline cervical secretion neutralized or even alkalinized the acid vagina), and had to migrate upward against a strong current. In both conditions the main and only important factor for transportation was the active motility of the spermatozoa. Such mechanisms as, for instance, the piston action of the penis, as described by J. Müller, the suction of the uterus during orgasm, as described by Wemich and Fehling, or the imbibition of the mucus plug with spermatozoa during orgasm and retraction after orgasm as described by Kristeller and Havclock Ellis, evidently played no role.

Seguy and Vimeux<sup>1</sup> point out that purulent cervical secretion is most unfavorable for the spermatozoa: "In certain women the cervical canal physiologically is never permeable for the spermatozoa, either because there is no thin mucinous secretion present, or because the secretion permanently is purulent. These facts may offer an understanding for certain unexplained cases of sterility." Similarly Kurzrock and Miller<sup>3</sup> emphasize the importance of the difference of electric potential between the vaginal and the cervical fluid causing a cataphoretic effect and say: "when the cervical mucus plug becomes infected it no longer shows the penetration phenomenon with semen," . . . and "if the cervical mucus is infected, very viscous, thick and opaque, the sperm in proximity to it will not accumulate at its boundary and will make no attempt to penetrate the mass."

Kurzrock and Miller<sup>3</sup> discovered another important factor for the passage of spermatozoa through the cervical canal, namely, the ability of the spermatid fluid to dissolve the mucus plug which physiologically protects the entrance of the external os. In cases of purulent cervicitis the mucus plug becomes resistant to the lysins of the spermatid fluid. "When frank pus was present, there was almost no digestion in 48 hours," and this explains the fact, that "a woman with an acute gonorrhea with its extensive purulent cervical discharge or with extensive leucorrhea due to tears or disease in the cervix almost never becomes pregnant as long as the discharge persists. Where the cervical mucus is only partially contaminated, considerable time may elapse before digestion is sufficient to allow spermatozoa to pass through the cervix. So that here, as above, by the time the spermatozoa have reached the tube their fertilizing power may be lost although their motility may remain. The patient remains sterile."

Many authors agree that purulent cervicitis and endometritis hamper and hinder the passage of spermatozoa through the cervical canal. In an exact analysis of this important cause of sterility, we must consider six points: (1) the current of the cervical and vaginal secretions, (2)

## ENDOMETRITIS AND TUBAL ECTOPIC PREGNANCY\*

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**T**HAT endometritis frequently produces sterility is an acknowledged fact. That tubal pregnancy occurs frequently within a Fallopian tube that is the seat of a chronic salpingitis is also conceded.

For pregnancy to occur in a tube that is chronically inflamed and not to occur in an endometrium that is the site of a similar pathologic process seems contradictory until all the facts are taken into consideration. In the case of the tube, only the fertilized ovum needs to be considered. Normally the ovum progresses down the course of the tube and into the uterus by passive motion, that is, by the action of the cilia of the tubal epithelium. However, should these cilia be destroyed or should sacs produced by adhesions within the tube be formed due to the inflammatory process, the progress of the fertilized ovum may be arrested and implantation may occur within the tube.

In contrast to the passive motion of the fertilized ovum, the spermatozoa are actively motile and this autonomous locomotion under normal conditions is controlled by two environmental factors. The first of these factors is called "rheotaxis" and is closely related to physiologic reflexes. Because of this so-called reflex the sperm cells move against the current of the cervical and vaginal secretions. The second factor is the biochemical composition of the medium, particularly its pH. The spermatie fluid itself is definitely alkaline, whereas the normal vaginal secretion is markedly acid. This acidity is hostile to the spermatozoa and paralyzes their motility. The vaginal acidity is high enough to exceed the alkalinity of the spermatie fluid and consequently, the mixture of spermatie and vaginal secretion is still of definite acidity. Seguy and Vimeux<sup>1</sup> determined the reaction of this mixture one-half hour after coitus as 6.1 to 6.2 pH. The normal cervical secretion is characterized by definite alkalinity, which by a process resembling chemotaxis, attracts the spermatozoa.

Seguy and Vimeux<sup>1</sup> describe a specific, thin cervical secretion produced by the cervical mucosa, especially at the time of ovulation, as being particularly favorable for the spermatozoa. The presence of this specific thin secretion at the time of ovulation offers very favorable conditions for the spermatozoa to penetrate the barrier of the cervix, thus facilitating fertilization at the time of ovulation. This observation by the two French investigators fits in very well with Knaus's theory of the coincidence of ovulation time and optimum fertilization time. However, the antagonistic influence of the acid vaginal secretion upon sperm migration should not be over-estimated. Spermatozoa if deposited at

\*Abstract of a case report presented at a meeting of the Chicago Gynecological Society, May 16, 1941.

In cervical purulent secretion only toxins produced by bacteria have to be considered. Rosenthal<sup>9</sup> made the interesting observation that not only acids, alkalies, salts of heavy metals, carbon dioxide, dyes and so on agglutinate spermatozoa, but some strains of *B. coli* similarly cause agglutination of spermatozoa, whereas *B. typhosus*, *B. paratyphosus*, *B. proteus*, *B. pyocyaneus*, *B. subtilis*, and *B. tuberculosis* have no such properties. Le Lorier and Fisch<sup>10</sup> found that toxins of twenty-day-old cultures of *B. coli* had the ability to agglutinate and to immobilize spermatozoa.

Since endometritis under special conditions apparently does not prevent the ascent of the spermatozoa, the latter may reach the tube and fertilize an ovum if present in the lumen. Precocious embedding of the fertilized ovum may then occur leading to a tubal pregnancy. Such cases of combined endometritis and tubal pregnancy are rare but deserve mention for they clinically support the experimental observation that migration of spermatozoa is not prevented by a medium of purulent inflammation.

#### CASE REPORTS

Recently we had the opportunity to study two cases in which a tubal ectopic pregnancy was found combined with a severe endometritis. The first case, endometritis postabortum and tubal ectopic pregnancy, was found at an autopsy performed in the morgue of the Cook County Hospital; the second, we owe to the courtesy of Dr. Werthammer, Huntington, W. Va.

**CASE 1.**—Colored female, 28 years of age, was admitted to the Cook County Hospital with the complaints of vaginal bleeding of six weeks' duration, cramping lower abdominal pain, fever, and abdominal distention for one week and fainting once during the week before admission. For one week prior to her entrance to the hospital the patient was treated at home by a physician with the daily administration of 10 c.c. of boiled milk intramuscularly and 10 c.c. of calcium glueonate intravenously. When she did not improve, she entered the Cook County Hospital.

The patient's past history revealed a miscarriage four months before her present illness, but she denied self-instrumentation. Otherwise her past history, as given, was negative.

She was admitted to a medical ward and six days later was transferred to a septic obstetric ward. Physical examination at that time revealed a temperature of 100.6° F.; pulse, 120; respirations, 24; blood pressure, 109/56. The conjunctivae were pale. Colostrum could be expressed from the left breast. The lungs, heart, and abdomen were essentially normal.

On pelvic examination the introitus was found to be multiparous, Bartholin's and Skene's glands and the urethra were negative, although a vaginal discharge was present. The external os barely admitted a small forceps. Pieces of tissue 1 to 2 cm. long and a few millimeters thick were protruding through the external os. The impression was that these were decidual tissue rather than placenta. The pathologist reported that they were portions of endometrium displaying a marked decidual reaction and a marked infiltration with polymorphonuclear leucocytes.

consistency of the cervical and vaginal secretions, (3) reaction of the cervical and vaginal secretions, (4) temperature of the cervical and vaginal secretions, (5) presence of leucocytes, (6) presence of spermatoxic substances.

1. The current of the cervical and vaginal secretions cannot be considered a definite hindrance since it is well known that a severe leucorrhea in many cases is not in itself a cause of sterility.

2. The consistency of the cervical mucus may serve as a hindrance in the case of a thick, very viscous plug of concentrated mucus as described by Kurzrock and Miller. But this does not hold when a thin, watery, purulent secretion is produced, as in some cases of acute cervicitis and endometritis.

3. The reaction of a purulent secretion is definitely alkaline. This holds true in general and has been proved in numerous cases of endometritis by Seguy and Vimoux. Consequently, purulent secretion should, at least by its reaction, facilitate the ascent and passage of spermatozoa.

4. The temperature of acute inflammatory tissue may rise even above the general temperature. Spermatozoa are delicate and sensitive to increased temperature as demonstrated by Stigler and recently by Weisman. But this holds only for increases of temperature of at least  $10^{\circ}$  or more, which far surpass those encountered in local inflammation which never amounts to more than 2 to  $3^{\circ}$ .

5. The presence of leucocytes in the vaginal and cervical secretions with specific reference to their influence upon sperm cells could not be found in the literature. However, communication with Dr. Abner Weisman of New York, who has carried out a great deal of experimental work on sperm cells, in the course of the last few years, and who has published a summary of this work in a monograph called *Spermatozoa and Sterility* (P. B. Hoeber, Inc., New York, 1941), reveals that he has tested the influence of pus cells on spermatozoa. He presented the results in an exhibit in the New York Academy of Medicine, Oct. 14 to 27, 1940, and in a short paper called "The Effect of Pus on the Survival of Spermatozoa," which is to be published soon. The sum and substance of his findings are that infection if it does inhibit sperm travel does so only by mechanical blockade due to the formation of pus clumps. Phagocytosis of spermatozoa by leucocytes does not occur, nor is their motility affected. "In vitro spermatozoa can live if mixed with pus 18 to 32 hours."

6. The presence of spermatoxic substances in the cervical and vaginal secretion and the effect which they have upon the sperm cells have been studied extensively. Metschnikoff deserves credit for having discovered the immobilizing spermatoxins produced by active immunization. Günther<sup>5</sup> in 1907 continued the investigations which Koelliker<sup>6</sup> started in 1856. He investigated the influence of more than 50 organic and inorganic compounds in various dilutions on the motility of fresh spermatozoa and demonstrated the particular high toxicity of chinin. The damaging influence of pure water on spermatozoa has recently been discovered by Weisman.<sup>7</sup>

I. Schiller and A. Giltcher<sup>8</sup> proved that in a nitrogen-free medium *B. subtilis* and some cocci produce lysin of spermatozoa, but not in normal saline solution: this observation does not meet with practical clinical conditions.

irregularly shaped, partially confluent foci of purulent necrosis. In the middle layer of the endometrium, remnants of necrobiotic decidua can be found. In some foci, shrunken chorionic giant cells can be seen. Some of the small arterioles and some of the glands are surrounded by thick coats of fibrin which similarly contain single shrunken chorionic cells, which are characteristic findings in endometritis postabortum (Fig. 1).



Fig. 2.—Endometrium, dense leucocytic infiltration and necrosis.  $\times 120$ .



Fig. 3.—Endometrium, in the lower part involuted Opitz glands, in the upper part inactive cytotogenic tissue with leucocytic infiltration.  $\times 120$ .

CASE 2.—Slides of this case (M. D.) were referred to the senior author for consultation. The patient was a white female, aged 37 years, who was admitted to the hospital on June 3, 1940, with the complaints of pain in the lower abdomen of three years' duration accompanied by chills and fever. These pains were sometimes very severe. More recently she was frequently nauseated and vomited and complained of anorexia. In addition there were complaints of weight loss and weakness. Her menses were regular and for the last several months had lasted for eight to ten days instead of three to four days as they had

The uterus was enlarged to about the size of a two months' pregnancy. The right adnexa revealed no masses or tenderness on bimanual examination. On the left side there was an indefinite fullness which was assumed to be a mass measuring approximately 5 by 6 cm. This mass seemed to extend into the cul-de-sac and produced a bulge that was very tender on palpation.

On the day of her transfer, six days after admission, a posterior colpotomy was done and old blood, both fluid and in clots, was recovered. Because of these findings a diagnosis of an ectopic pregnancy was made and a left salpingectomy was performed on the same day.

At operation a tubal pregnancy that had ruptured through the isthmic portion of the left Fallopian tube accompanied by a massive hemoperitoneum was noted. The right adnexa and the left ovary were reported to be in good condition. The pathologist reported an acutely infected ectopic pregnancy.



Fig. 1.—Endometrium, foci of necrosis with leucocytic infiltration, in the center remnants of decidua with chorionic invasion.  $\times 120$ .

Postoperatively the patient developed a bronchopneumonia. Ten days postoperatively foul pus drained through the lower part of the incision. The temperature postoperatively was septic in character; the course was progressively downhill and the patient died three weeks after operation.

The laboratory workup revealed the urine to be negative for albumin and sugar. The blood findings were as follows: the hemoglobin, 34 per cent; red blood count, 1,980,000; white blood count, 12,100; two weeks later the hemoglobin, 54 per cent; red blood count, 3,160,000; white blood count, 9,700.

*Microscopic Description.*—The myometrium presents a moderate edema of the intermuscular connective tissue septa as is usually found in and after pregnancy. The number of the vessels are increased, the smaller vessels are markedly tortuous. The endometrium shows in the deeper layers cystically dilated glands with flattened epithelium and cloudy debris in the lumina. The cytogenic tissue is densely infiltrated with leucocytes and this inflammatory infiltration increases toward the upper part of the mucosa, which is replaced by a thick coat of fibrin, with leucocytes in the interstices of the network. There are numerous



tically twice as high, 32 per cent in the convulsive group and 35 per cent in the nonconvulsive group. The incidence of permanent hypertension increases almost proportionately to the number of subsequent pregnancies. Of the 42 women who had other pregnancies, 23 or 54 per cent had toxemia with their later pregnancies. It seems then from these findings that an individual, who as a primipara has a toxemia of pregnancy, has a 50 per cent chance of a toxemia with a subsequent pregnancy and at the same time is enhancing the possibility of a permanent hypertension with each succeeding pregnancy.

In our follow-up studies, an effort was made to find some correlation between the average normal weight of the individual, the weight gain during the pregnancy, and the incidence of subsequent hypertension, but no constant relationship could be determined. Likewise, an attempt was made to ascertain any causal relationship between urinary tract infections and the appearance of hypertensive toxemias, but no constant association could be found on the basis of our examinations and review. At times infections of the upper urinary tract were found in association with toxemia, but even more frequently urinary tract infections occurred without any evidence of hypertensive toxemia, while the toxemias commonly occurred without any of the common clinical or laboratory evidence of infection in the urinary tract. There was nothing in our studies to suggest that pyelitis or pyelonephritis played any constant or significant part in either the causation of the toxemia or the frequency of the residual hypertension.

#### SUMMARY

The hypertensive toxemias of pregnancy seem to be characterized essentially by a generalized arteriolar spasm. If the spasm is neither too severe nor too prolonged, the patient may have a complete recovery afterward without any evidence of permanent damage, and pass through additional pregnancies uneventfully. On the other hand, recovery may seem complete, but the toxemia recurs in a subsequent pregnancy, while in others various degrees of hypertension persist, and occasionally a malignant type of vascular renal disease may ensue with a fatal outcome in a fairly short space of time. In our attempts to carry out follow-up studies on 483 patients who had had toxemia of pregnancy from one to thirteen years previously, 7 were known to have died, presumably of vascular renal disease. Of the 224 patients who were re-examined 104, or 46 per cent, had hypertension on the basis of the commonly accepted criteria for hypertension. Of the 42 women who had had pregnancies subsequent to their first pregnancy with toxemia, 54 per cent had toxemia with their later pregnancies, while on the other hand 46 per cent had repeated their pregnancies without a recurrence of the toxemia, and 53 per cent had a normal blood pressure at the time of the follow-up examination.

The age and parity of the patient at the time of the toxemia seem to be the most significant factors in the incidence of subsequent hypertension: the younger the patient the less the chances of permanent hypertension, whereas the older the patient the greater the chances, approximately 80 per cent of those above thirty-five years of age having hypertension. The primiparous patients have an incidence of hypertension of

previously. There was no vaginal discharge. The patient's past history was negative; she had one child 14 years old, who was in good health.

On physical examination an adenoma of the thyroid, the size of an egg, was palpable on the right side. The abdomen was everywhere tender and rigid. The liver, spleen, and kidneys were not palpable, but there was tenderness over both lumbar regions. A vaginal examination was not done.

The blood count showed a hemoglobin of 69 per cent; red blood cells, 3,650,000; white blood cells, 14,000; the differential count revealed: polymorphonuclear leucocytes, 80 per cent; lymphocytes, 17 per cent; and monocytes, 3 per cent. The urine contained 2-plus albumin, and there were many red blood cells and a few white blood cells and epithelial cells.



Fig. 4.—Tube, in the upper part, the thinned muscularis, in the lower part, placental villi and chorionic masses.  $\times 120$ .

On the day following admission dilatation and curettage were done, and the pathologic report stated that the endometrium was of premenstrual type and no evidence of pregnancy was noted. A week later a left salpingo-oophorectomy and right salpingectomy were performed. The surgeon reported old blood and serum in the abdominal cavity with a ruptured right tubal pregnancy and a left pyosalpinx. The patient was discharged from the hospital as improved three weeks after admission.

The uterine scrapings were submitted to the senior author for microscopic examination, and he noted that there was no decidual reaction, but that there was a dense infiltration of inflammatory cells in the cytogenic tissue. The epithelium of the glands was high columnar and secreting. The lumina of the glands contained pale pink-staining secretion mixed with numerous leucocytes. The cytogenic tissue was very cellular, dense, and markedly infiltrated with leucocytes. In many areas the endometrium was undergoing necrobiotic changes and was being transformed into amorphous, pale, pink-staining masses, which were densely infiltrated with leucocytes many of which were pyknotic. A few pieces of tissue reveal such purulent, necrotic tissue exclusively with additional infiltration by red blood corpuscles (Figs. 2 and 3).

A section through the tube shows a typical tubal pregnancy with an empty collapsed amniotic cavity 11 mm. in diameter. There is a semi-circular hematoma between the placenta and the tubal muscularis, which in one area is densely infiltrated by leucocytes. Over about a quarter of the periphery the tubal wall is thinned out to a few layers of muscle cells. The placental villi, mostly well preserved, present a well-developed Langhans layer and contain no vessels (Fig. 4).

#### DISCUSSION

Physiologically we find in tubal ectopic pregnancy a decidual reaction of the endometrium analogous to the decidual transformation of the endometrium in intrauterine pregnancy. This decidua is cast off as a triangular sac after the rupture or abortion of the ectopic pregnancy, that is, as soon as contact between placenta and maternal tissue is severed. In both of our cases no actual decidual reaction of the endometrium could be found. The few foci of decidual reaction in the first case are invaded by chorionic cells. This proves that they are remnants of the previous intrauterine pregnancy. The absence of actual decidual response to the present ectopic pregnancy can be explained as caused by the endometritis which paralyzes the cytogenic cells and prevents them from responding normally to the hormones of pregnancy. Similarly in endometritis of the nonspecific generalized type, not in the focal type seen in tuberculosis, the phases of the menstrual cycle generally are suppressed and even in the premenstrual phase of highest activity, in an inflamed endometrium, tortuous and secreting glands usually are not to be seen. In the first case the chorionic cells prove that the decidua originated from the previous intrauterine pregnancy and not from the present ectopic one.

Both cases give evidence that even severe endometritis offers no unsurmountable hindrance for spermatozoa to ascend and to reach the tubes. Even the roughening of the endometrial surface and the presence of necrobiotic, cellular debris in the endometrial cavity may not prevent the migration of the spermatozoa. But, on the other hand, in cases of cervicitis when the inflamed mucosa produces thick mucin which plugs the cervical canal and at the same time is resistant to the lysins of the spermatozoa, or when clumps of pus cells obstruct the external os, complete obstruction may occur. The larger diameter of the endometrial cavity leaves enough space for the ascent of the spermatozoa even in the presence of a severe suppurative and necrotizing endometritis. Although frequently cervicitis and endometritis develop coincidentally, there is no evidence of such a coincidence in the two cases. Endometritis after abortion, as in the first case, generally has no tendency to extend to the cervical mucosa. Doubtless conditions for intrauterine embedding of the ovum become unfavorable in case of an inflamed endometrium, although inflammation as a hindrance to implantation should not be over-estimated, since we occasionally find tubal implantation in the course of a rather severe salpingitis.

#### CONCLUSION

Endometritis in general prevents intrauterine implantation of the fertilized ovum, but as our two cases prove, it may not prevent sperma-

tozoa from migrating through the uterine cavity and fertilizing the ovum in the tube.

## REFERENCES

- (1) Seguy, I., and Vimeux, J.: *Gynéc. et obst.* 27: 346, 1933. (2) Kurzrock, R., and Miller, E. G.: *AM. J. OBST. & GYNEC.* 24: 19, 1932; 15: 56, 1928. (3) Kurzrock, R., and Miller, E. G.: *Proc. Soc. Exper. Biol. & Med.* 24: 671, 1926-27. (4) Weisman, A.: *Spermatozoa and Sterility*, New York, 1941, Paul B. Hoeber. (5) Günther, G.: *Arch. f. d. ges. Physiol.* 118: 551, 1907. (6) Koelliker, A.: *Ztschr. f. wissenschaft. Zool.* 7: 1856. (7) Weisman, A.: *Urol. & Cutan. Rev.* 44: 387, 1940. (8) Schiller, Ign., and Giltseher, A.: *Centralbl. f. Bakt. I. Abt.* 109: 428, 1928. (9) Rosenthal, L.: *Proc. Soc. Exper. Biol. & Med.* 28: 827, 1930-31. (10) Le Lorier and Fisch: *Gynéc. et obst.* 20: 596, 1929.

## ENDOMETRIAL POLYPOID FIBROSARCOMA

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THIS report is given for two reasons. First, there was a distinct discrepancy in the clinical diagnosis and the microscopic report in a case of recurring endometrial polyposis. As proved eventually, at the time of removal of the uterus, the clinical diagnosis of sarcoma was correct. Second, we feel that we are dealing with a definite clinical and anatomic picture which, apparently, is not sufficiently known. From the experience in our own laboratory, corroborated by the relative paucity of reported observations similar to ours, this disease, which clinically may be designated best as recurring massive endometrial polyposis of elephantiastic character, apparently is relatively rare. It was not until the uterus was removed that the clinical diagnosis of sarcoma could be confirmed histologically. At the same time, in spite of reported recurring endometrial polyps over a period of three and one-half years, there was no clear gross evidence of any actual invasive growth of this endometrial sarcoma into the myometrium. Even in the polypous tumor material removed in fair-sized pieces two months previous to the extirpation of the uterus, a definite diagnosis of sarcoma could not be made from a large number of sections taken from different parts. Our diagnosis was confirmed by Robert Meyer who was kind enough to lend us his most valuable support.

We are in the fortunate position of being able to correlate all histologic findings secured at different times over a period of three and one-half years, with the final picture taken from the extirpated uterus.

## CASE REPORT

Mrs. M. B., 52 years old, white, married, a patient of Dr. James King, entered the Buffalo General Hospital on Oct. 20, 1937, with the following history: her chief complaint was brownish, stringy discharge from the vagina of six weeks' duration. Her last menstrual period was in December, 1936. She had apparently been well until she noticed this scant, foul-smelling, brownish, stringy discharge. There were no complaints of pain but itching and irritation of the skin adjacent to the

vagina were present. Thirteen days before admission to the hospital the discharge increased in amount, requiring one perineal pad during the day and one at night. Three days before admission she noticed a mass protruding from the vagina.

The past history revealed a loss of 50 pounds in weight during the past ten years; otherwise the remainder of the history was not pertinent except for diabetes, treated by diet and insulin therapy.



Fig. 1.

Fig. 1.—Very low power view of the entire polyp.

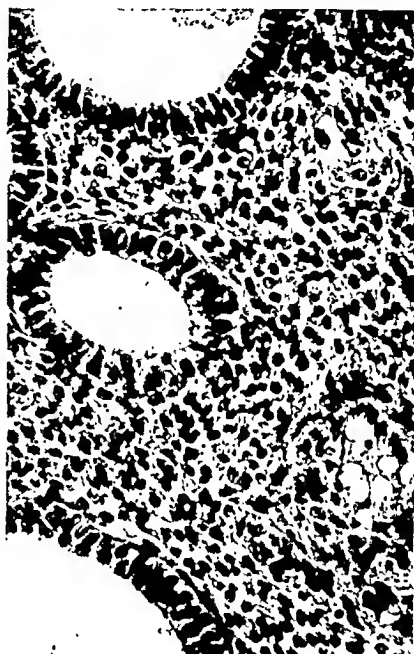


Fig. 2.

Fig. 2.—Medium power view of a typical part within the polyp.

The physical examination was not remarkable except for a diffusely enlarged thyroid gland and the gynecologic examination which revealed a necrotic, infected, prolapsed uterine polyp.

On Oct. 21, 1937, under cyclopropane anesthesia, the polyp (Fig. 1) was removed and the cavity of the uterus was packed with gauze. An uneventful recovery followed.

Microscopic diagnosis was that of a typical glandular, cystic endometrial polyp (Fig. 2) which was not malignant. A smaller fragment from the cervix showed slight edema and fibromatous hyperplasia of the stromal cells.

The patient's next admission was Sept. 26, 1938; approximately one year later. She complained now of a polyp protruding from the introitus, which had been bleeding for two or three days before admission.

Under cyclopropane anesthesia, a broad fingerlike polyp was removed from the lower uterine segment. The cervix was dilated and a polyp forceps, introduced into the cavity, brought away several polyplike structures, the largest of which was the size of a walnut. The patient was discharged in good condition on the third day.

*Pathologic Diagnosis.*—Gross inspection revealed four edematous polyps measuring from 3.5 by 2 cm. to 5.5 by 3 cm. in thickness. Microscopic examination showed glandular cystic cervical polyps with marked edema of the stroma (Fig. 3) and injection of the capillaries, slight hemosiderosis, and slight hyalinization. The glands contained mucoid secretion. In one of the polyps there were scattered atypical endothelial cells in the stroma. No reference was made to malignancy.



Fig. 3.

Fig. 3.—Medium power view of the somewhat fibromatous and edematous portion of the polyp near the surface epithelium.

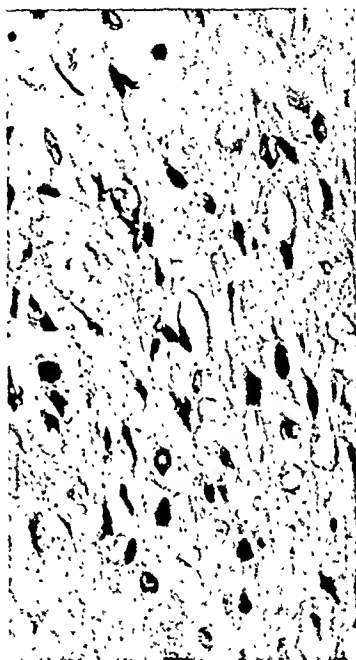


Fig. 4.

Fig. 4.—Medium power view, showing a fibromatous portion of the polyp with distinct edema.

Patient's third admission was Aug. 5, 1940, three years after the removal of the first polyp. At this time her history revealed the interesting fact that on seven different occasions polyps described as "the size of a finger" had been removed by her physician in his office. One week before this admission the patient complained of cramplike lower abdominal pains and again the presence of a mass protruding from the vulva. Bleeding of moderate degree was also present.

On the day following, under cyclopropane anesthesia, an olive-sized, gangrenous appearing polyp was removed from a wide base at a point midway up on the right side of the uterine cavity. A number of smaller polyps were easily removed with the ring forceps. Radiation with radium (500 mg. hours) was given.

*Pathologic Diagnosis.*—Specimens include several polyps from uterus and several large fragments of tissue. On cut section tissue was soft and grayish yellow in color with extensive hemorrhages present.

Microscopic diagnosis revealed markedly edematous polyps, containing a moderate number of glands. The surface epithelium was still preserved, with occasional papillary protrusions. A number of recent hemorrhages were present. Some of the sections showed a marked preponderance of stroma with almost fibromalike structures (Fig. 4).

Her last admission was Dec. 27, 1940. At this time she complained of having had occasional "spotting" since her last admission. A yel-

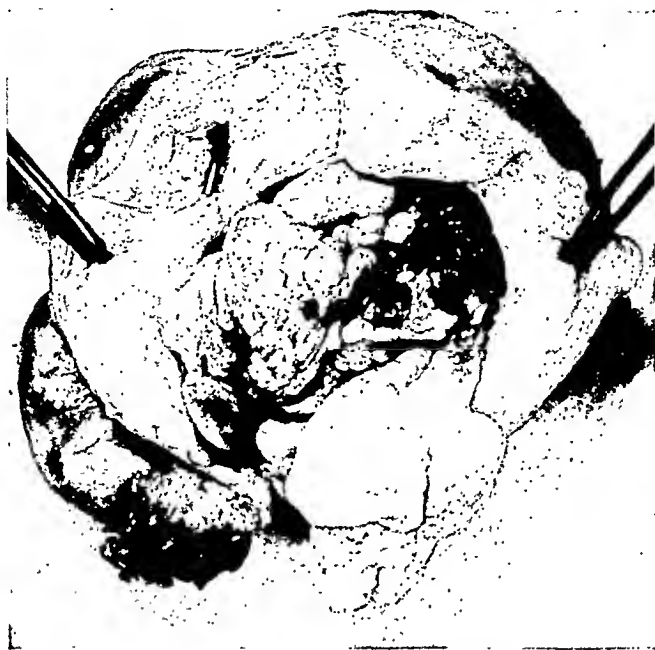


Fig. 5.—Opened uterus with the cavum almost completely filled by huge, slightly lobulated polyps.



Fig. 6.—Sagittal plane through the uterus, showing intramural fibroids and huge polyps with hemorrhages, especially in the protruding one.

lowish discharge was also present. Once again she complained of protruding masses from the vagina. On this admission she showed symptoms of hyperthyroidism and for the first time her diabetes presented difficulties in management and, while waiting for its control, additional polypoid tissue was removed on three different occasions. Finally on Jan. 23, 1941, under avertin-cyclopropane anesthesia, a supravaginal hysterectomy was performed by Dr. James King. The specimen which was removed forms the basis for the present study.

*Macroscopic Examination.*—(Figs. 5 and 6.) Polypous and papillary, firm structures, measuring 10 by 7 by about 2 cm. Amputated corpus uteri, already dissected; weight 430 Gm. (measurements of entire specimen 10 by 12.5 by 7 cm.). Showed several pea to lemon size, subserous fibroids with hyalin and calcific degeneration in the two larger ones. Within the cavum uteri was suspended a huge, papillary, polypous mass of endometrial tissue, in some places distinctly hemorrhagic. Base of this mass was apparently firmly adherent to the uterine wall.



Fig. 7.—Very low power view through one of the huge polyps and the myometrium close by, including one intramural fibroid.

*Microscopic Examination.*—On a section taken through the bulk of the polyp, including its stalk and the adjoining wall of the uterus (Fig. 7), the following picture was seen: The stroma of the polypous structure was made up of proliferating mesenchymal cells, many of which had the form of long spindle-shaped fibroblasts. In many areas there was far-progressed production of collagenous fibers with hyalinization and also quite diffuse necrosis. Near the surface epithelium, as well as in the deepest areas, and most marked in the stalk, there was a frankly sarcomatous picture consisting of spindle-shaped cells as well as polymorph cells and quite a number of giant cells containing from 2 to 4 closely packed nuclei (Figs. 8, 9, 10, and 11). Here and there the delineation between myometrium and endometrium was indistinct and especially the sarcomatous portions seemed to infiltrate superficially the myometrium close by. Glands were scattered over the substance of the huge polypous structure in relatively small numbers. Some of them were evidently compressed while a few were somewhat cystically dilated. They were lined by columnar epithelium which in the dilated glands was





Fig. 8.

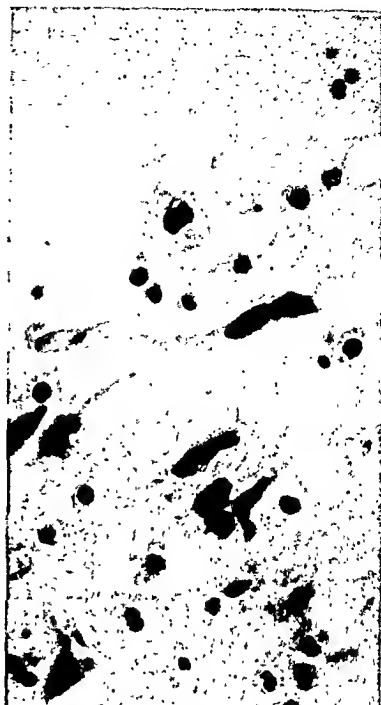


Fig. 9.

Fig. 8.—Medium power view of the sarcomatous polyp, including a deep endometrial niche lined in part by metaplastic squamous epithelium. The lower part to the left shows frankly sarcomatous, the upper to the right a simple fibromatous and markedly edematous, pattern.

Fig. 9.—High power view of a fibromatous polyp with edema.

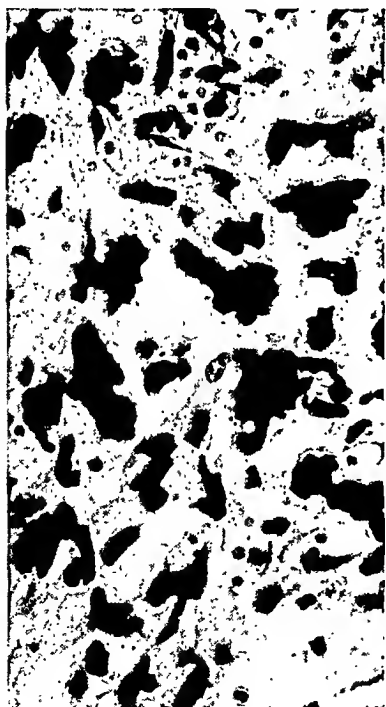


Fig. 10.

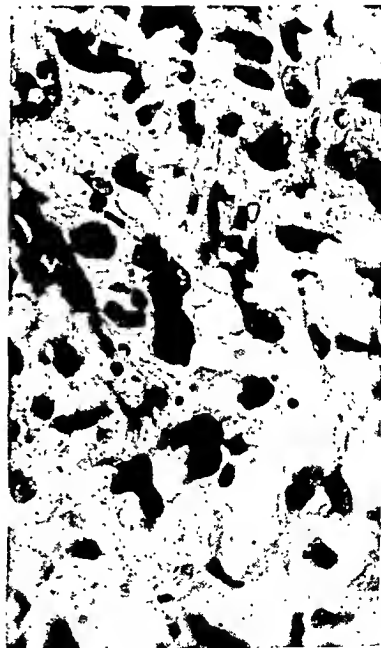


Fig. 11.

Fig. 10.—High power view of a sarcomatous section with many peculiarly shaped giant cells.

Fig. 11.—High power view of an area of edematous, fibromatous structures merging with sarcomatous giant cells.

flattened by pressure. The surface showed hyperplastic squamous epithelium, in some areas with attempts at keratinization. The fibroids in the wall were rather cellular but otherwise typical leiomyomas. The fibrosarcomatous proliferation was, for the most part, limited to the stroma of the endometrium. Again in many areas the complete hyalinization and absence of any atypical cell was bringing about a rather complex histologic picture on a cross section through the entire polyp. Finally there were many recent hemorrhages in the subepithelial surface areas and also occasional evidence of previous hemorrhages in the form of hemosiderin globules free and in huge macrophages.

*Diagnosis.*—Sarcomatous endometrial polyposis, in some areas of mature, plain fibromatous pattern with elephantiasis-like edema and with localized necrosis.

#### DISCUSSION

In searching the literature for this type of apparently relatively benign, endometrial, sarcomatous polyposis, we found only a few cases which seem to correspond to ours. Fellander<sup>1</sup> in his report of a case of polyps of the uterus speaks of "elephantiasis endometrii fibrosarcomatosa gigantocellularis." The patient was forty-eight years of age and complained of a bloody discharge for more than four months, following her last menstrual period. A polypoid transformation of the entire endometrium was found. One hazelnut size and one walnut size polyp, and in addition one 1 cm. long polyp about the thickness of one's index finger, were described. All of the polyps were rather soft and some showed hemorrhagic infarction in their distal end. One had a central cyst. There was no invasion into the myometrium. Microscopic examination of this tissue showed many benign looking, fibrillar structures in which there were occasional giant cells. This, it was felt by Fellander,<sup>1</sup> did not conform to the usual picture of sarcoma. Therefore, he called it elephantiasitic fibrosarcoma. This patient was followed for seven years; she remained in good health and had no recurrence. Wollgren<sup>2</sup> described a similar case but without giant cells. One case which, we feel certain, is very similar to ours, is the second case in the series "polypoid adenoma of the uterus" by Strong.<sup>3</sup> The entire mucosa of the uterus was replaced by a polypous, villous growth. It is interesting to note that in a number of sections a mere adenomatoid picture of the uterine mucosa was seen. The stroma in these sections was rather fibrous, but in some other, separately received, sloughed off tumor particles there was a more solid mass of cells with great irregularity and many giant cells and only traces of glands. This tumor recurred in the stump in four months and grew rapidly. It was checked by radium for a time but not lessened. Figs. 4, 5, and 6, from Strong, prove better than the description, the sarcomatous nature within glandular polyposis in his case. In Novak's recent edition on *Gynecologic and Obstetric Pathology*,<sup>4</sup> we find the following statement on endometrial sarcoma: "The endometrial sarcoma not infrequently assumes a polypous architecture." According to Novak, the sarcomatous polyps are bulkier, denser, and more friable than the common benign variety. In this connection we wish to state that in our case close, careful gross inspection of the many polypous pieces received previous to the total extirpation of the uterus in no way revealed a sarcomatous character. Our impression was rather that of chronic edema in fibromatous polyps. Unconsciously following the terminology used in the scanty literature

on this type of tumor, our report used the same gross and histologic descriptive criteria which are apparently characteristic of these recurring polyps, namely, the elephantiasis-like picture.

Our impression that this peculiar polypous type of endometrial sarcoma is apparently uncommon or possibly not recognized even in a large amount of material is supported by the absence of this type in a series of 20 cases of sarcoma of the endometrial stroma reported by McDonald, Broders and Counseller<sup>5</sup> from the Mayo Clinic.

The clinical course preceding the extirpation of the uterus and the gross picture with but superficial infiltrative growth in association with the histologic picture tending in many areas toward firm fibrosis, lead us to expect a favorable prognosis for our patient as far as recurrence or metastases from this sarcoma are concerned.

Re-examination of all previous slides leads to the following conclusions: the histologic picture of an edematous fibrosarcoma was unquestionably present already at the first examination more than three years previous to extirpation of the uterus. In some areas of the polyps removed from the extirpated specimen there are almost identical pictures with those seen at the first and second examination. In fact, the few atypical cells, which at that time were thought to be endothelial cells, seem in one polyp to be really young, large, atypical fibroblasts. These same cells are massed in considerable numbers in the frankly sarcomatous areas seen in the basal parts of the polyp within the extirpated uterus. It was apparently confusing that this so-called fibromatous polyp was seen together with a typical glandular adenomatous polyp within the same curetting, and in this latter typical glandular polyp there is no evidence of fibromatous proliferation of the stroma. It is very impressive now in re-examining all the slides that the endometrial stroma had changed in all polyps into a firm, proliferating, fibroblastic blastoma with very distinct tendency to hyalinization and with that highly characteristic circulatory disturbance which is responsible for the elephantastic appearance and which is caused by chronic edema. It is this intercellular fluid which gives the tumor cells frequently a stellated appearance, and this might explain that some pathologists use the term of fibromyxosarcoma which, however, hardly seems justified, as there is no true mucin like there is in a real myxoma.

The extensive necrosis seen in a few polyps removed two months preceding the extirpation of the uterus did not change our initial impression of an entirely benign tumor, inasmuch as in the nonnecrotic parts the histologic type was that of an entirely mature fibroblastoma with hardly any irregularity in size and chromatin content of nuclei.

Clinical course, as well as the ultimate picture of a good-sized polyp firmly fixed within the endometrium of the wall of the uterus, justify the conclusion that this endometrial polypoid sarcoma has a very marked tendency to fibrotic regression, in spite of the fact that it is a continuously, actively proliferative, true sarcoma of fibroblastic type with considerable tendency to formation of giant cells. It is expected that after this total extirpation of the uterus the course of the patient should be uneventful. We feel the name of massive, polypoid, elephantastic fibrosarcoma of the endometrial stroma designates the most conspicuous gross and histologic characteristics of this tumor.

The authors wish to express their appreciation to Dr. James King and to Dr. Kornel Terplan under whose direction this paper was prepared.

26 per cent, while toxemia in the multiparous patient is followed by an incidence of 66 per cent. Pregnancies subsequent to the toxemic pregnancy seem to be definite factors, for when pregnancy is repeated in the patient who has had toxemia, the chances of later hypertension are twice as great as in those who do not repeat their pregnancies, and the risk is increased with each subsequent pregnancy.

The severity and the type of the toxemia, except instances of previously known chronic nephritis or essential hypertension, seem of no special significance in the frequency of hypertension. There is a lower incidence following eclampsia, but the tendency of eclampsia to occur in the young primipara and the higher primary mortality rate in the severe forms of eclampsia are probably the factors which are operating to explain in some degree the difference in incidence of hypertension following the convulsive and nonconvulsive types. The height of the systolic and diastolic pressures at the time of the toxemia, except at the very high levels, seem to play only a small part in the incidence of later hypertension.

Except in cases of previously known nephritis and hypertension, there are no definite criteria by which the possibility of permanent hypertension following the toxemia can be predicted with certainty, although, in general, the chances are much less in the young primipara, whereas the chances in the older multiparous individuals, particularly those who repeat their pregnancies, are much greater. The individual who has had toxemia should be observed afterward, and if hypertension persists, additional pregnancies should be undertaken with considerable reluctance and with a very careful prenatal regime. On the other hand, about half of the patients will have no persisting hypertension and may go through subsequent pregnancies without ill effects or permanent damage.

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## PROTEIN AND HEMOGLOBIN IN NORMAL AND TOXIC PREGNANCIES

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IT IS now believed that the edema so commonly seen in toxic pregnancies is due in part to hypoproteinemia which results from dietary protein deficiency.<sup>1, 2</sup> Experiments on dogs<sup>3</sup> have shown that the protein intake is not only related to the production of serum protein but also related to the production of hemoglobin. In this work, protein and hemoglobin were removed from the circulation of some of the animals, while in others the hemoglobin in the form of washed red cells was re-injected and their only loss was in the plasma. Thus, in certain respects, the rapidly increasing removal of all the products necessary for its growth by the fetus from the maternal circulation was simulated.

This study was undertaken, therefore, with the purpose of investigating the relationship of the diet to anemia and hypoproteinemia and of their relationship to the occurrence of the toxemias of pregnancy.

eases of hydatidiform mole, found only one of these in the Fallopian tube. King<sup>11</sup> reported one case of tubal mole, and emphasized the value of the Aschheim-Zondek test as an aid in diagnosis. Four other scattered reports of single cases have also appeared in the foreign literature.

A recent paper by Hertig and Edmonds<sup>12</sup> on the "Genesis of Hydatidiform Mole" summarizes the results of a study of a large number of aborted (uterine) specimens. These authors feel that, although the typical advanced intrauterine mole of pregnancy is a relatively rare disease (1 in 2,062 deliveries), not enough emphasis has been placed on the origin and evolution of hydatidiform changes in early pathologic pregnancies. They found pathologic or so-called "blighted" ova in almost 50 per cent of spontaneous abortions in their material. They describe in detail their classification of these, and the transitional changes observed in early hydatidiform degeneration. It has been noted that pathologic embryos (and often absence of embryos) are frequently found in tubal pregnancies, and these pregnancies are of necessity relatively early. It seems probable that hydatidiform changes are present in tubal pregnancies more often than is generally believed, and the possibility should be kept in mind.

We wish to report a case which falls, we believe, in the category of true hydatidiform moles and not in the transitional group. The three accepted characteristics of this condition are present: (1) Trophoblastic proliferation, (2) liquefaction and degeneration of the villous stroma, and (3) scantiness or absence of blood vessels in the villi.

The history is as follows: A 29-year-old white married woman was admitted to the Albany Hospital, on the Service of Dr. M. J. Stapleton, on Aug. 17, 1938. Her chief complaint was of right-sided lower abdominal pain of one week's duration. She had been married for seven years and had never become pregnant. Her menstrual periods had always been regular, occurring every twenty-eight days, lasting two days, and being accompanied by moderate dysmenorrhea.

Her last regular period had occurred on May 30, 1938. She missed the June period, and on July 7 she started to have moderate vaginal bleeding. The bleeding was thought to be her normal period as she had the mild abdominal cramps which usually occurred at this time. However, she continued to bleed intermittently during the rest of July, requiring 2 pads daily. At no time was the hemorrhage severe. She continued also to have occasional cramps, but no incapacitating pain.

By August 11, the bleeding had decreased. The abdominal pain became localized to the right lower quadrant and was now almost constant. It increased in severity during the following week, and increasing constipation developed. The patient worked as a practical nurse until the day before admission. She then called a doctor, who sent her at once to the Hospital.

Examination of the patient revealed a uterus of normal size, a tender mass in the right adnexal region, and a normal left vaginal vault. Her general physical condition was good, admission temperature 99° F., pulse 90, and respirations 20. The red count was 3,400,000, and the white count 10,000. The blood Wassermann test was negative. No preoperative Aschheim-Zondek test was done. A diagnosis of ectopic pregnancy was made and a laparotomy performed.

At operation, a mass 3 cm. long, with a diameter of 2.5 cm., was present in the midportion of the right Fallopian tube. The tubal serosa over this mass was bluish in color but showed no evidence of perforation. A

## REFERENCES

- (1) *Fellander, J.*: Arch. f. Gynäk. 144: 83, 1907. (2) *Wollgren, A.*: Monatschr. f. Geburtsh. u. Gynäk. 626: 10, 1899. (3) *Strong, L. W.*: Am. J. Obst. 79: 502, 1919. (4) *Novak, E.*: Gynecological and Obstetrical Pathology, Philadelphia, 1940, W. B. Saunders Company, p. 188. (5) *McDonald, J. R., Broders, A. C., and Counsellor, F. S.*: Surg., Gynec. & Obst. 70: 223, 1940.

## HYDATIDIFORM MOLE FOLLOWING TUBAL PREGNANCY

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PRIOR to June, 1938, only 35 cases of primary chorionepithelioma of the Fallopian tube had been reported.<sup>1</sup> Since that time, however, the reports of 7 more cases have appeared. In view of the number of cases of this malignant tumor, it is surprising to find so few recent reports of hydatidiform mole following tubal pregnancy. In theory, this lesion should be many times more common than chorionepithelioma. Meyer<sup>2, 3</sup> in 1918, and Mall and Meyer<sup>4</sup> in 1921, in reviewing the material of the Carnegie Embryological Collection, stressed the fact that early changes characteristic of hydatidiform mole are frequently overlooked, both in aborted material from the uterus and in specimens of tubal pregnancy. Hydatidiform mole may, therefore, occur more frequently than is usually supposed.

A review of the literature as far back as 1918, has been made in an attempt to arrive at an estimate of the incidence of primary tubal mole. There is considerable difference of opinion as to the criteria for diagnosis in borderline cases, both in tubal and in uterine mole. Therefore, the figures given for the incidence of these conditions vary widely with different authors.

Ewing<sup>5</sup> mentions 12 cases of chorionepithelioma following pregnancy in the Fallopian tube, but does not speak of tubal mole. Goodall<sup>6</sup> in the Davis *Obstetrics and Gynecology*, states that hydatidiform mole primary in the tube is exceedingly rare, but gives no specific details. Schumann<sup>7</sup> in the Curtis *Obstetrics and Gynecology*, remarks that in theory tubal mole should be fairly common. In estimating its incidence, Schumann, as well as Novak,<sup>8</sup> quotes the statistics previously given by Meyer<sup>2</sup> in 1918. The latter author<sup>2, 3</sup> found 7 cases in the literature and added 48 of his own. Three years later, in collaboration with Mall, Meyer<sup>4</sup> gave the incidence of hydatidiform degeneration in tubal pregnancies as 34 per cent, or 45 cases out of 153 studied. His diagnostic criteria, according to Novak,<sup>8</sup> however, were open to question, since he based his conclusions on the presence of certain stromal and vascular changes believed by him to be characteristic of early mole. These changes alone are not accepted by all pathologists as definite evidence of mole formation. His percentage may, therefore, be presumed to be somewhat high. In the opinion of Phaneuf,<sup>9</sup> hydatidiform degeneration occurs in about 3 per cent of all cases of tubal pregnancy, but he gives no specific data concerning actual case histories. In this same paper, Phaneuf reports 9 cases of mole seen in his personal experience, all of which were of intrauterine origin. Sherman<sup>10</sup> in a report of 78

is no definite tissue culture-like growth of detached masses of chorionic epithelium. There is little penetration of the tubal wall in the sections studied.

In conclusion, because of the recent interest in tubal chorionepithelioma, it seems timely to report this case of hydatidiform mole primary in the Fallopian tube.



Fig. 3.



Fig. 4.

Fig. 3.—Area "A" in Fig. 2. Note the marked proliferation of the chorionic epithelium, especially the Langhans' cells. The stroma shows liquefaction degeneration and no blood vessels are seen in these villi. *Syn.*, Syncytium; *Lan.*, Langhans' cells; *St.*, stroma. (X66.)

Fig. 4.—Area "B" in Fig. 2. This section through the mole shows marked proliferation of the trophoblastic elements, especially the syncytium. *Syn.*, Syncytium; *Lan.*, Langhans' cells; *St.*, stroma. (X66.)

The unusually marked proliferation of the chorionic epithelium covering the villi in this case would make one suspicious of malignant potentialities in this tumor.

The author wishes to thank Dr. M. J. Stapleton for his permission to use the clinical history of this case, and Drs. A. W. Wright and C. F. Graham for their helpful advice.

#### REFERENCES

- (1) *Pearse, R. L., and Fraser, C. K.*: AM. J. OBST. & GYNEC. 35: 1046, 1938.
- (2) *Meyer, A. W.*: Am. J. Obst. 78: 641, 1918. (3) *Meyer, A. W.*: Surg. Gynec. & Obst. 28: 293, 1919. (4) *Mall, F. P., and Meyer, A. W.*: Contrib. Embryol. No. 56 12: 233, 1921. (5) *Ewing, J.*: Neoplastic Diseases, Ed. 1940, p. 640. W. B. Saunders Co. (6) *Goodall, J. R.*: Davis Loose-Leaf Obst. & Gynec. 2: 22. (7) *Schumann, E. A.*: Curtis Text Ob. and Gyn., 1933 Ed., ii, 966. (8) *Novak, E.*: Gynecological and Obstetrical Pathology, 1940, W. B. Saunders Co., p. 438. (9) *Phaneuf, L. E.*: New England J. Med. 217: 770, 1937. (10) *Sherman, J. T.*: Am. J. Surg. 27: 237, 1935. (11) *King, W. W.*: Clin. J. (Brit.) 61: 238, 1932. (12) *Hertig, A. T., and Edmonds, H. W.*: Arch. Path. 30: 260, 1940.



small intramural myoma was present in the right cornu of the uterus. Right salpingectomy, myomectomy, and appendectomy were done. The patient made an uneventful convalescence.

On gross section, the dilated portion of the Fallopian tube contained granular friable material, portions of which were described as cystic. No fetus was seen.

On microscopic section, the tubal mucosa showed a marked inflammatory reaction, and many polymorphonuclear leucocytes were seen in the lumen of the tube. The site of the pregnancy showed markedly swollen chorionic villi in some areas, with liquefaction and degeneration of the stroma (Figs. 1 and 2). Other villi were sur-



Fig. 1.



Fig. 2.

Fig. 1.—Section through tubal wall, mucosa and hydatidiform mole. The tubal mucosa is acutely inflamed. The swollen avascular villi and masses of proliferated chorionic epithelium are characteristic of hydatidiform mole. See Figs. 3 and 4. *Syn.*, Syncytium; *Lan.*, Langhans' cells; *St.*, stroma. (X11.)

Fig. 2.—Section through another portion of the hydatidiform mole. Note the masses of Langhans' cells and of syncytium. The stroma of the villi shows liquefaction and blood vessels are scanty or absent. *Syn.*, Syncytium; *Lan.*, Langhans' cells; *St.*, stroma. (X11.) Area "A" magnified X66 is seen in Fig. 3, and Area "B" magnified X66 is seen in Fig. 4.

rounded by piled-up masses of Langhans' cells and syncytium (Figs. 2, 3, and 4). No blood vessels were seen in these villi, although the duration of the pregnancy was ten to eleven weeks. Because of the striking hyperplasia of the chorionic epithelium, the possibility of malignancy, either actual or potential, was brought to mind.

A two-year follow-up on the patient showed that she presented no further symptoms, and a recent negative Friedman test tends to confirm the diagnosis of benign hydatidiform mole, rather than the malignant or so-called destructive mole. There is no evidence of invasion of the villous stroma by chorioepithelial elements. The Langhans' cells and syncytium, although markedly hyperplastic, are rather evenly arranged, and do not vary much in size, shape, or staining reaction. There



chest showed atrophy of the breasts with distribution of hairs particularly about the areola. The lung findings were normal. On percussion the heart was found to be within normal limits; on auscultation a soft systolic murmur was heard over the apex and aortic areas.

The abdomen was distended and a distinct fluid wave was elicited. The liver, kidneys, and spleen were not palpated. In the lower abdomen a hard, ballotable mass about the size of a five and one-half months' pregnancy was palpated. The gluteal regions showed slight atrophy of the fat tissue, and there was slight pitting edema of the legs.

Pelvic examination revealed a slight hypertrophy of the clitoris. The introitus admitted two fingers with ease. The Bartholin and Skene's glands and urethra were negative. Vaginal examination, following abdominal paracentesis in which 8,500 c.c. of a straw-colored fluid was removed, revealed a softened, lacerated cervix pointing posteriorly and to the right. The corpus uteri was fairly firm and not enlarged. A smooth, moderately firm, nontender mass the size of a five months' pregnancy was palpated. It was difficult to determine whether this mass was attached to the uterus or lay adjacent to it. The mass was somewhat movable and the adnexal structures were obliterated by the mass.

*Laboratory Findings.*—Red blood cell count was 3,800,000 per cubic millimeter; hemoglobin 72 per cent; white blood cell count was 11,500; differential count revealed 87 per cent polymorphonuclear leucocytes, 10 per cent lymphocytes, and 3 per cent monocytes. The Kahn and Wassermann tests were negative. The urine was negative for sugar and albumin.

X-ray films of the chest showed a small amount of infiltration in the lungs, probably due to passive congestion. X-ray picture of the abdomen showed no radio-opaque shadows.

In view of the clinical and physical findings, a masculinizing tumor of the ovary was considered by Dr. H. Isaacs of the Medical Department.

The patient was transferred to the Gynecological Service of one of us (A. E. K.), and she was operated upon on Aug. 20, 1940. A right ovarian tumor the size of a five months' pregnancy was exposed following the removal of 10,000 c.c. of yellow serous ascitic fluid. The uterus was enlarged to the size of a two months' pregnancy. A bilateral salpingo-oophorectomy and a supracervical hysterectomy were performed; 1000 c.c. of saline were instilled into the abdominal cavity before closure.

The patient made an uneventful recovery and six weeks after her operation the hairs of the chest and chin disappeared and the clitoris returned to normal. No ascites was noted since the operation.

*Pathologic Report.*—The specimen consisted of a uterus amputated above the cervix, both tubes, and both ovaries. The uterus, previously opened, measured 7 by 6 by 4 cm. The myometrium measured up to 2.5 cm. in thickness; the consistency was firm and light tan gray in color traversed by grayish white lines. The endometrium measured up to 1 mm.; it was firm and reddish gray in color. The fimbriated ends of both Fallopian tubes were patent. The walls were slightly thickened and the mucosa was light gray in color.

The left ovary measured 3.5 by 2.1 cm. On section it contained a previously opened cyst filled with a brownish serous fluid and numerous corpora albicantia. The right ovary was transformed into a tumor mass and measured 15 by 17 by 11.5 cm. Except for a 7 cm. circular area which was roughened, the surface of the ovary was smooth and

## ARRHENOBLASTOMA OF THE OVARY

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**B**ECAUSE of the relative infrequency of masculinizing tumors of the ovary, this case is worth reporting. Novak<sup>1</sup> has gathered a total of 51 cases. Since then cases have been reported in the literature by Canelo and Lisser,<sup>2</sup> Dockerty and MacCarty<sup>3</sup> and others.

Meyer,<sup>4</sup> who has contributed considerably to the recognition of this unusual type of tumor, points out the variability of the histologic findings of arrhenoblastoma. Novak,<sup>5</sup> in his description of arrhenoblastomas, describes three types of histologic variations, namely the highly differentiated form (testicular adenoma of Pick), the highly undifferentiated variety in which the histologic picture resembles that of a sarcoma, and the third form which is termed the intermediate group whose diagnostic criteria, such as tubule formation and occurrence of interstitial cells, are developed to a greater or lesser degree.

We would like to report a case showing the intermediate type of arrhenoblastoma of the ovary. The patient, E. B., 47 years of age, was admitted to the Cook County Hospital on Aug. 7, 1940. She stated that she was perfectly well until February, 1940, when she first began to experience backaches. These pains were fairly mild until March 4 of the same year when they became more severe and at the same time her abdomen became distended. On March 22, 1940, her physician tapped her abdomen and removed a considerable amount of yellow fluid. This relieved her pain considerably. The patient found it necessary to be tapped on three other occasions before entering the hospital for further treatment. In the past six weeks she has noted a slight growth of hair in the chin area associated with fall of hair from the head.

The patient's menses began at 15 years and 4 months of age; the frequency was regular, every twenty-eight days, up to August, 1939. The flow was profuse for the first two days and tapered off gradually, the entire period lasting eight days. One week after cessation of the normal flow in August, 1939, a slightly bloody flow was noted and this lasted for two days and ceased. Thereafter the patient menstruated regularly until January, 1940, when she developed an amenorrhea until Aug. 7, 1940, the day she entered the hospital. At that time she had a scanty flow.

The patient was pregnant one time and delivered spontaneously, the labor period lasting only three and a half hours.

Physical examination revealed a well-developed, well-nourished white woman lying comfortably in bed and not acutely ill. The pulse was 96, the temperature 99.4° F., respirations 24, and the blood pressure 108/80. The scalp was normal. Pupils reacted to light and accommodation; there was a slight suggestive lid lag and exophthalmus. The chin showed a slight hirsutism. The thyroid was not palpable. The



Fig. 2.



Fig. 3.

Fig. 2.—Hemalum eosin stain photomicrograph showing papillary racemose-like gland structure. (Mag.  $\times 76$ .)

Fig. 3.—Hemalum eosin stain showing large dilated glands lined by high cuboidal epithelial cells containing amorphous debris in the lumen and the small tubular glands in the center lined by low cuboidal epithellum. (Mag.  $\times 76$ .)

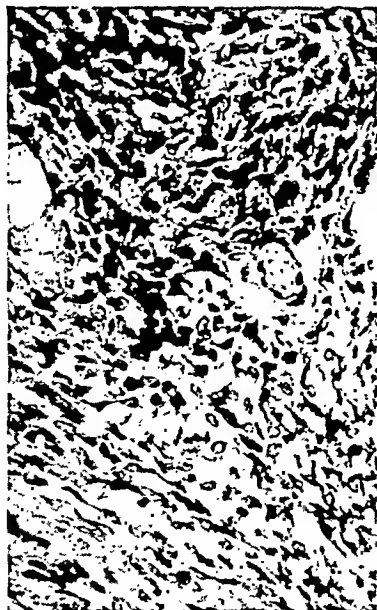


Fig. 4.



Fig. 5.

Fig. 4.—Hemalum eosin stain showing clumps of foam-like cells in the interstitial tissue resembling the interstitial cells of Leydig. (Mag.  $\times 320$ .)

Fig. 5.—Hemalum eosin stain showing atrophy of the endometrium and single cystic endometrial gland. (Mag.  $\times 76$ .)

light purplish-red in color. The sectioned ovary was composed of a mushlike purplish gray to greenish gray necrotic tissue which in places, particularly in the center of the mass, was partially liquefied (Fig. 1). In other places in the periphery of the tumor where the tumor tissue was not degenerated, ill-defined nodular areas light yellowish gray mottled by areas of purplish gray color were noted.

Microscopic examinations were made from different areas of the ovarian tumor as well as from the opposite ovary and from the uterus. The sections were stained with hemalum and eosin, azocarmine, Van Gieson, sudan III, Gamori, Mallory phosphotungstic hematoxylin, and iron hematoxylin. In addition, unstained frozen sections of the tumor were studied by means of the fluorescence microscope.<sup>6</sup>



Fig. 1.—Cut section of arrhenoblastoma of ovary showing cystic areas in the tumor due to liquefaction of necrotic tissue.

Throughout the ovarian tumor, in addition to large focal areas of necrosis, there were seen several different types of glandular arrangement. One type was composed of a papillary process which in places appeared to show fusion of the processes forming small racemose-like structures (Fig. 2). These glands were lined by several layers of cuboidal epithelial cells. The cytoplasmic membranes of those cells were rather indistinct. The nuclei were round to oval shaped and coarsely granular. Other glands were distended, round to oval in shape (Fig. 3) and were lined by single layers of high cuboidal cells with fairly large round nuclei which were distinctly vesicular but in places resembled the cell lining described in the glands above. The cytoplasm of some of these cells contained sudanophilic droplets, and nearly all of the cells contained phosphin 3 R droplets as demonstrated by the fluorescence microscope. The lumina of these dilated glands were filled with desquamated cells whose nuclei had undergone pyknosis and karyorrhexis and contained also amorphous debris and coagulated pink-stain-

## FIBROSARCOMA OF THE BUTTOCK ASSOCIATED WITH PREGNANCY

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THESE two cases are reported because of the rather unusual association of fibrosarcoma of the buttock and pregnancy. The cases varied widely as to treatment and outcome.

The first case is unusual in that the tumor arose in the gluteal region, and by direct extension encroached upon the birth canal. Dystocia due to tumors, of course, is not rare, but most often the tumor arises from a pelvic structure, myomata,<sup>1</sup> ovarian tumor,<sup>2</sup> or the bony pelvis itself.<sup>3</sup> The second case presented no dystocia.

CASE 1.—B. H. (No. 2335), a 42-year-old white gravida, was first seen in the clinic at the Hospital, Dec. 18, 1940. She was referred by her family physician because of a painful swelling in the left buttock which appeared as a small lump three and one-half years previously. Following an unsuccessful attempt at excision elsewhere six months previously, the tumefaction had evinced accelerated growth. Histologic examination by the consulting pathologist showed a sarcoma.

Examination revealed a moderately anemic and emaciated woman. A hard, irregular, tender mass approximately 15 cm. in diameter which was fixed to the skin but not to the bone presented in the left buttock. The mass invaded deeply into the gluteal muscles and ischiorectal fossa medially to the vaginal wall with resultant narrowing of the outlet and vagina. The patient was found to be seven months pregnant; the expected date of confinement was estimated as being Feb. 27, 1941. The patient had had four previous pregnancies, all of which were normal and terminated in uneventful deliveries. The fetal position was occiput anterior; the head was floating and fetal heart tones were normal. Pelvic measurement revealed a diagonal conjugate of 12.5 cm. The tuberosities could not be accurately measured because of tumor growth over the left tuberosity; however, the distance between the right tuberosity and the resistant borders of the neoplasm on the left was approximately 5 cm.

The patient was admitted to the hospital Jan. 11, 1941, with no change in the above findings except for some increase in size of the tumor which was not rebiopsied here because of a desire to avoid a fungating mass through the incision. The fetus was found to be viable. Roentgenograms revealed no evidence of local or remote osseous involvement. The Kahn was negative.

It was the consensus of opinion that the malignancy was advanced beyond any hope of effective specific therapy, the presenting problem therefore being salvage of a live infant. It was further felt that this would be jeopardized if the forces of labor were allowed to impinge the fetus against the narrowed and very resistant outlet. The patient was consequently treated supportively.

ing material. The third type of gland was small and at times distinctly tubular in character. They were lined by low cuboidal epithelium (Fig. 3) whose cytoplasm was more pale than the larger glands described above. The nuclei, however, were similar to the nuclei of the first group of glands described, except possibly for a more marked elongation. The interstitial tissue for the most part was composed of a loose edematous connective tissue which was quite cellular and contained few reticulum fibrils scattered throughout the interstitial tissue. Particularly in the region about the smaller glands were single or groups of foamlike cells (Fig. 4) filled with sudanophilic material which was rich with a bright green-fading vitamin A fluorescence as demonstrated by the fluorescence microscope. After the fading of the vitamin A fluorescence, a stable brownish ultraviolet fluorescence remained. In addition, anisotropic lipid droplets were present in these cells. These cells resembled the interstitial Leydig cells of the testicle. The capsule of the tumor was composed of edematous connective tissue and had completely lost the characteristic appearance of the cortex of the ovary.

Section of the other ovary revealed numerous corpora albicantia and no apparent primordial ova in the cortex. In one area was a small cyst lined by large cells, containing brown pigment granules.

Section of the uterus revealed an atrophy of the endometrium (Fig. 5) with single large moderately dilated glands lined by a tall columnar epithelium containing more or less centrally placed round to oval-shaped vesicular nuclei. The endometrial stroma appeared to be moderately fibrotic. The myometrium was unchanged.

In view of the above pathologic finding, a diagnosis of an intermediate type of arrhenoblastoma was made.

#### SUMMARY

A case of an arrhenoblastoma of the ovary is reported. It is characterized clinically by symptoms of defeminization as characterized by atrophy of the breast and fat of the gluteal region and symptoms of masculinization as characterized by hirsutism and hypertrophied clitoris. From a pathologic point of view, the diagnosis of arrhenoblastoma of the ovary is greatly enhanced by the use of the fluorescence microscope which enables one to demonstrate more definitely those cells which resemble the interstitial cells of Leydig as seen in a testicle.

#### REFERENCES

- (1) *Novak, E.*: AM. J. OBST. & GYNEC. 36: 840, 1938.
- (2) *Canelo, C. K., and Lisser, H.*: Endocrinology 24: 838, 1939.
- (3) *Dockerty, M. B., and MacCarty, W. C.*: Surg., Gynec. & Obst. 68: 767, 1939.
- (4) *Meyer, R.*: AM. J. OBST. & GYNEC. 22: 697, 1931; Beitr. f. Path. Anat. 84: 485, 1930.
- (5) *Novak, E.*: Gynecological and Obstetrical Pathology, Philadelphia, 1940, W. B. Saunders Company, p. 357.
- (6) *Popper, H., and Ragins, A. B.*: Arch. Path. 32: 258, 1941.

Since the prenatal clinic of the Philadelphia General Hospital accepts only those on relief or in quite similar financial circumstances, it was assumed that little animal protein food could be purchased, since this is one of the most expensive items in an ordinary diet. Dietary protein deficiencies were expected.

### METHOD

Serum protein and chemical hemoglobin determinations were made on each new prenatal clinic patient. If the hemoglobin was low, a red cell count was done. Out of the new cases for each day, 3 were chosen to be followed with repeated determinations, namely, the one with the lowest protein, the one with the lowest hemoglobin, and the one with a normal value in both. A dietary survey was made for as many of these cases as possible. A qualified dietitian gave each woman a form to be filled out with the quantities of all foods eaten for a week. Many of the patients were irresponsible and illiterate, so that only a few could be successfully followed and only a few (71 cases) returned the diet sheets in any form that was good enough for analysis by the dietitian.

Patients were admitted for toxemia when the systolic pressure reached 100, or when other symptoms appeared in sufficient degree to warrant admission. Serum protein, a/g ratio and hemoglobin determinations were made on admission. No attempt was made to suggest therapy, either in the clinic or on the ward.

### FINDINGS

About 20 per cent of the prenatal clinic patients showed a protein of 6.0 Gm. or less on their first visit. The protein findings are usually arranged so that the values for patients in the same month of pregnancy appear together.

TABLE I. THE OCCURRENCE OF HYPOPROTEINEMIA IN CLINIC PATIENTS BY MONTHS

Month of pregnancy	2	3	4	5	6	7	8	9
Total number of patients studied for protein	22	43	73	91	69	64	43	51
Per cent with low protein	18.1	9.3	16.5	15.5	23.1	17.1	23.2	25.4

There were a number of women who remained well while their protein levels were low, but there were also a number who had more or less marked symptoms of toxemia. In the line which shows the percentage of the low group (6 Gm. or less) who were toxic, the number was highest in the group found low in the fifth month but remained high for all the succeeding months.

TABLE II. THE OCCURRENCE OF TOXEMIAS AMONG THE LOW PROTEIN GROUP

Month of pregnancy	2	3	4	5	6	7	8	9
Percentage of the low group who were toxic	0	25	50	69.2	50	36.6	33.3	26.0

When the patients were divided into a group who became toxic and a normal group, it was found that the number with hypoproteinemia was greater in the former than in the latter. After the protein levels of the two groups had remained the same, viz., between 6.6 and 7.5 Gm. for the first seven months of pregnancy, the level of the toxic group fell below that of the normal group, which remained at the previous level to the end.

The results of determinations repeated three or more times on each patient appear in Tables IV, V, and VI. In the first two of these tables, low protein means that one or more values of 5.6 Gm. or less was obtained in the time stated. In the third, low protein means that the average of all determinations during pregnancy were low.

The patient spontaneously entered into active labor Feb. 7, 1941, the membranes rupturing very shortly thereafter. The patient was taken to the operating room immediately and given 150 mg. of novocaine intrathecally. Low cervical transverse cesarean section was performed without technical difficulty. A normally developed viable male infant was delivered. Before the procedure was completed the blood pressure dropped to 70/40 notwithstanding two administrations of  $\frac{3}{4}$  gr. of ephedrine, and extreme circulatory collapse with anoxemia and coma intervened from which the patient at no time aroused. Blood transfusions, stimulants, and nasal oxygen were employed to no avail. The patient died thirty hours following the section presenting throughout this interval the syndrome described above.

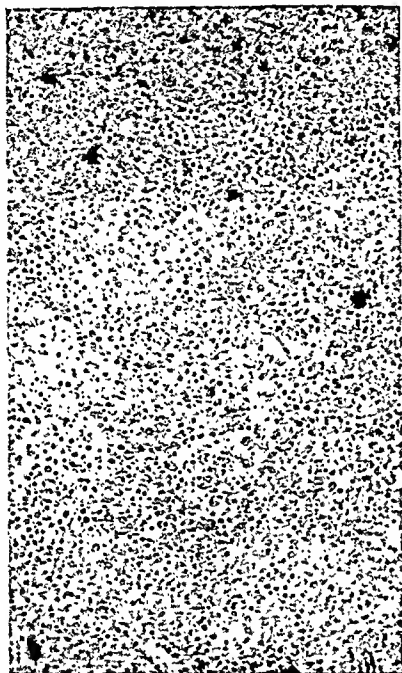


Fig. 1.

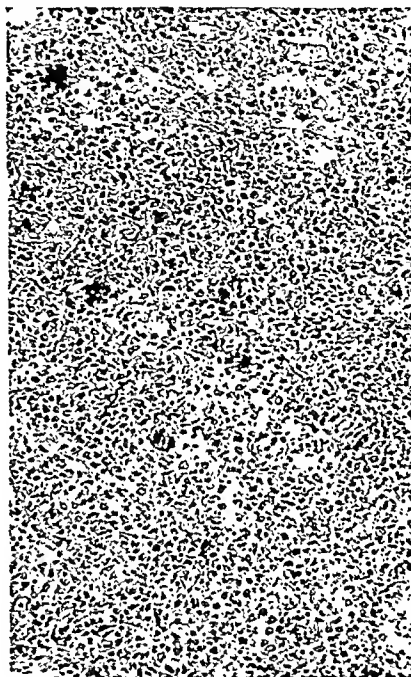


Fig. 2.

Fig. 1.—(No. 41-A-199.) Liver,  $\times 55$ . *Diagnosis:* Early atrophy, red stage. Note loss of structure with necrosis of liver tissue and infiltration with polymorphonuclear leucocytes.

Fig. 2.—(No. 41-A-199.) Thigh, soft tissue,  $\times 55$ . *Diagnosis:* Very cellular malignant sarcoma with little stroma and numerous tumor giant cells.

*Autopsy.—Anatomic Diagnosis:* Fibrosarcoma of the thigh; edema of the cervix and vagina; hypertrophy of the uterus (post partum one day); multiple splenic infarcts; acute yellow atrophy of liver.

The body was that of an extremely anemic, white, adult female. The breasts were enlarged, and on cut section showed a yellowish white material oozing from the prominent lobulated breast tissue. On the inner upper surface of the left thigh there was a fungating, ulcerating tumor mass. This was grayish red in appearance, soft in consistency, and it invaded the neighboring muscle. It showed marked evidence of necrosis and hemorrhage, but did not involve the bone. The peritoneum contained a small amount of clotted blood. There were a few areas in the bases of both lungs suggesting early bronchopneumonia. The spleen weighed 320 Gm. and showed multiple areas of recent infarcts. The liver weighed 1,700 Gm. It was somewhat soft in consistency, had



rounded edges, and was brownish yellow in color. On section the architecture was quite clearly delineated. There were numerous poorly defined, small, yellow zones within the liver parenchyma. The uterus was enlarged, the vagina and cervix edematous.

Microscopic examination showed evidence of bronchopneumonia. There were multiple areas of recent infarction in the spleen. The liver showed recent widespread areas of necrosis. These zones were scattered in a haphazard fashion throughout the liver parenchyma (Fig. 1). There was no evidence of regeneration of liver cells, and only very rare zones of hemorrhage. The liver cells in the regions of necrosis showed the disappearance of their nuclei and many of the cells were completely destroyed. The kidney showed fairly marked tubular degeneration. The uterus showed the characteristic changes one day post partum. Sections from the tumor showed a very cellular fibrosarcoma. Tumor giant cells were numerous. The nuclei of the cells were rich in chromatin, and showed many fine nucleoli. There was evidence of old and recent hemorrhage, and there was invasion and destruction of muscle (Fig. 2).

The tumor, a fibrosarcoma, showed no evidence of metastases. The liver atrophy was acute, widespread, and probably the immediate cause of death. The bronchopneumonia was an incidental and terminal finding.

CASE 2.—L. H. (No. 2092), colored female, aged 20 years, was first seen at the Cancer Hospital on Sept. 25, 1940, complaining of a tumefaction of the left buttock of five months' duration which first appeared following trauma. There had been increasing local pain which radiated down the posterior aspect of the lower extremity. Ambulation had been progressively impeded, and when seen at this time the patient was able to walk only with the aid of crutches. There had been a 22-pound weight loss since the tumor had first been noticed. There was a history of recent irregular menses, and the patient had been amenorrheic during the past two or three months. She had had one previous pregnancy which was normal.

Examination revealed a well-developed and well-nourished girl in apparent good general condition. On the left posteriorly, at the level of the gluteal fold, there was a firm, smooth, globular tumefaction, 12 cm. in diameter which felt fixed and remained immobile on rotation of femur. There was a marked limp due to pain and stiffness in the hip region. Examination further revealed evidence of a three and one-half months' pregnancy.

Routine laboratory procedures gave results within normal limits except for a moderate secondary anemia. The blood Kahn was negative. Roentgenogram of the hip revealed no bony changes, the tumefaction throwing a soft tissue shadow overlying the lateral aspect of the left hip joint and greater trochanter. Complete skeletal roentgenograms revealed no evidence of metastases. An approximate three to four months' fetal skeleton was visualized in the pelvis. The mass was biopsied at which time it was found to be encapsulated and, in part, cystic. The capsule was found to be inseparably attached to the capsule of the hip joint and to extend medially to the ischial spine from which it could not be separated. Histologic examination of the obtained tissue revealed a very cellular fibrosarcoma in which mitotic figures were infrequent (Fig. 3). It was felt that the only surgical approach of curative adequacy would

be hemipelvectomy. Because of disadvantages of this procedure and because of the marked cellularity of this tumor, x-radiation was favored.

Consequently the patient was given 2,000 roentgens x-radiation through each of four  $10 \times 15$  cm. portals directed at the lesion at 50 cm. STD. (200 KV, 1 mm. copper, 1 mm. Al.). The patient stood the radiation well. She was discharged Nov. 15, 1940, at which time she was completely free of pain and was able to walk well. There was still minimal drainage through the biopsy wound.

When seen March 5, 1941, the tumor was observed to have markedly decreased in size. The incision was well healed. The fetus was found viable, in L.O.P., head floating.

On April 4, 1941, elsewhere, the patient spontaneously delivered a living female infant, which was apparently normal in every respect. The patient was seen in the clinic, along with her baby, on May 9, 1941. At this time palpation revealed the tumor to be firmer and slightly larger than on March 5, 1941. The patient was advised to enter the hospital for x-ray therapy to two new ports. She promised to enter in one week, but up to the present time, she has not returned, nor has the social service department been able to contact her.

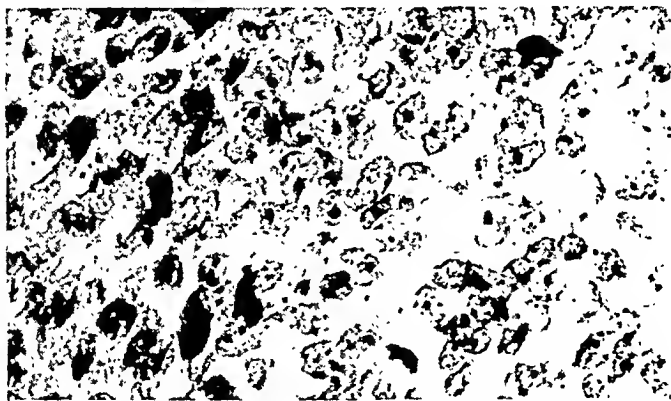


Fig. 3.—(No. 40-1468.) Buttock, soft tissue,  $\times 240$ . *Diagnosis:* Fibrosarcoma. Very cellular, rapidly growing sarcoma with numerous mitotic figures.

#### DISCUSSION

In the first case, the tumor involved a large portion of the buttock near the pelvic outlet. It was obviously an inoperable lesion. The question arose as to whether x-radiation should be attempted. It was felt that this course of treatment would be purely palliative since fibrosarcomas do not, as a rule, respond well to x-radiation. Walther<sup>4</sup> reports 13 per cent of five-year cures with x-ray therapy, and states that the best results were with fibrosarcomas of the eyes, ears, oral cavity, mesopharynx, and mediastinum. Paterson<sup>5</sup> makes the statement that x-radiation is actually contraindicated for fibrosarcoma unless given as a palliative procedure. X-radiation of the tumor would have exposed the fetus to x-rays since the tumor extended into the pelvis. Mundell<sup>6</sup> has pointed out the dangers to the fetus of exposure to x-radiation. For these reasons it was decided to aim only at obtaining a live infant.

The second case represented a different problem. The patient presented herself earlier in pregnancy with a much more circumscribed tumor. The tumor, moreover, was situated so that x-radiation could be given without exposing the fetus to any of the primary beam, and to

very little scattered radiation. It was felt, therefore, that the mother deserved a thorough attempt at curative irradiation. Surprisingly enough, the tumor responded well, perhaps because of its marked cellularity.

One of the most unusual features of the first case is the acute yellow atrophy, which probably accounted for the patient's death. Rolleston<sup>7</sup> states that he has seen this disease only 13 times in thirty-four years, except when it was caused by specific poisons, such as arsphenamine, etc. This patient received no medication which could have been the etiologic factor. Barbiturates were not used, and the anesthesia was spinal. Apparently this was a case of acute yellow atrophy resulting from a combination of the pregnancy and the tumor. Until the cesarean section was done, however, there were no signs or symptoms of toxemia. Malignancy in itself, even when in the form of a rapidly growing sloughing tumor, does not cause acute yellow atrophy.

The diagnosis of acute yellow atrophy was not made before death, since the patient did not live long enough to develop jaundice.

#### REFERENCES

1. *Pinard*: Ann. de gynec. et d'obst. 55: 165, 1901.
2. *Heil*: München. med. Wehnschr. 51: 282, 1904.
3. *Stadfeld*: Zentralbl. f. Gynäk. 4: 417, 1880.
4. *Walther*: Strahlentherapie 64: 59, 1939.
5. *Paterson*: Brit. J. Radiol. 12: 526, 1939.
6. *Mundell*: AM. J. OBST. & GYNEC. 13: 86, 1927.
7. *Rolleston*: Oxford Medicine, New York, 1920, 3: Oxford University Press.

4852 MARYLAND AVENUE

## BASAL CELL CARCINOMA OF THE VULVA\*

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THIS study concerns itself with basal cell carcinoma of the vulva, which is one of the rarer types of malignant neoplasms of the vulva. It is based on the study of 4 such cases occurring on the clinical service and private practice of Dr. Fred J. Taussig. The clinical cases were all observed since 1927 at The Barnard Free Skin and Cancer Hospital.

Following are the histories and findings in these cases of basal cell carcinoma of the vulva:

CASE 1.—Mrs. M. S., a 72-year-old white woman, came to the Barnard Hospital Clinic because of an irritation on the left side of the vulva of twelve years' duration. She had 11 children and her menses ceased at the age of 57. This area of irritation ulcerated intermittently, causing an intense pruritus of the vulva. No bleeding was associated with this. The lesion began about the size of a small pea and continued to grow very slowly. Physical examination revealed a superficial ulcer about the circumference of a silver dollar at the upper angle of the left labium majus (Fig. 1). The ulcer involved the mucous membrane of the prepuce. The ulcer was not infiltrating in nature and the edges were hard and rolled. The base

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of the ulcer showed no attachment to the underlying tissue. A diagnosis of carcinoma of the vulva was made. There was no evidence of regional glandular involvement at this time. On Sept. 1, 1927, a vulvectomy was done. The lesion on the left upper half of the vulva was removed with a good surrounding margin of normal skin. The leucoplakic area over the labia minora was also removed from the level of the urethral meatus upwards.

*Pathologic Examination* (Dr. L. H. Jorstad).—"The specimen is that of an irregularly-shaped portion of skin from the vulva, measuring 4 by 7 cm. Part of the section is covered with mucous membrane and part with skin. At the mucocutaneous margin is an ulcerated area, irregular in shape,  $1\frac{1}{2}$  cm. in diameter. The edge of a portion of the ulcer is thickened and the remainder of the edge is smooth. The thickened edge is grayish white in color. The remainder of the ulcer is brownish gray in color and roughened. On section the whole area is made up of opalescent, fibrous tissue with no extension into the subcutaneous tissue. Microscopically, the section shows the edge of the ulcer which is sharply demarcated from the adjacent



Fig. 1.—Photograph of vulvar lesion (Case 1), involving the left labium majus and minus and prepuce.

skin. The epidermis at this point is thickened. At the base of this ulcerated area there are collections of epithelial cells which are basal in origin. There is no invasion of these cells below the subcutaneous tissue. There is a moderate amount of plasma and round cell infiltration present in the connective tissue." (Fig. 2.)

*Diagnosis.*—Basal cell carcinoma of the vulva.

Two years later the patient reported back to the hospital for observation, at which time several enlarged lymph nodes were felt in both inguinal regions. A bilateral Basset operation was done on Dec. 6, 1939, by Dr. Taussig. At the time of operation it was noted that there was only a slight lymphatic enlargement and only little evidence of malignant invasion on either the right or the left side. Pathologic examination of the lymph nodes showed nests of cells which were entirely different from the cells in the remaining portion of the gland. No definite mitotic figures were seen. These nests of cells were hypertrophic germinal centers. There was no disturbance in the normal architecture of the lymph glands. No evidence of malignancy was noted. The patient developed some fever on the first postoperative day and developed some moisture at the lung bases. She began to fibrillate and show signs of cardiac decompensation. She died on the tenth postoperative day. No post mortem was obtained.

CASE 2.—Mrs. R. A., a white married woman, aged 63 years, was treated at the Barnard Hospital in 1931 for multiple basal cell epitheliomas of the face and neck. In May, 1933, she developed several superficial ulcerative lesions on the mons veneris and on the left labium majus. They were treated by local excision and suture. Pathologically they showed small nests of cells composed of, for the most part, basal

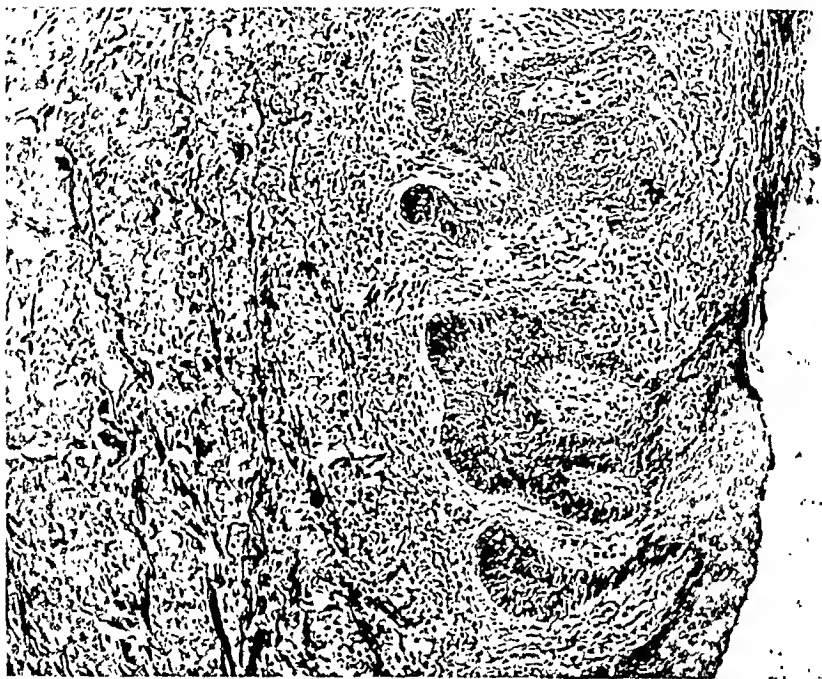


Fig. 2.—Section taken at margin of vulvar ulcer (Case 1), showing early basal cell carcinoma. There is some thickening of the epidermis present.



Fig. 3.—Showing cystic degeneration in the center of the islets of basal cells, giving rise to a cystic basal cell carcinoma (Case 2).

cells. These nests were compact, but occasionally showed some cystic degenerative areas in the center. The diagnosis was made of cystic basal cell carcinoma (Fig. 3). On Jan. 22, 1941, this patient was seen again and there was no evidence of recurrence.

CASE 3.—Mrs. G. K., a 42-year-old, white, married woman, came to the Barnard Hospital Clinic in July, 1932, complaining of a growth on the external genitalia. The lesion had been present for four years and had resulted in some bleeding. Physical examination was negative except for the pelvic findings. The patient showed an everting, hard nodule, red, with superficial leucoplakic spots on the nodule. The vulvar skin was normal. The left femoral glands were enlarged. The right-sided glands were not palpable. A diagnosis was made of carcinoma of the vulva (relatively benign). A bilateral Basset operation for removal of the inguinal-femoral lymph glands and a cautery vulvectomy were done. Microscopically the tissue showed cells grouped in masses of varying sizes and shapes. These cell



Fig. 4.—Showing ulcerated basal cell carcinoma involving the left labium majus and minus (Case 3).

masses lay in a bed of connective tissue. The cells were from the basal layer of the epithelium, and there was no tendency to invasion of the surrounding tissue. No metastases were found in the lymph glands. The patient's postoperative course was uneventful and she was discharged from the hospital in good condition. She was seen in September, 1940, at which time she showed no clinical evidence of recurrence.

CASE 4.—(Private case.) Mrs. G. A., a 63-year-old married white woman, complained of pruritus vulvae for the past twenty years and for the past three years noticed a growth in the left labium majus. She had used many different salves and ointments without any perceptible change. The lesion bled frequently and was tender at various times. It had not greatly increased in size in the past few years. She had no inguinal pain or adenopathy.

*Physical Examination.*—General physical examination was essentially negative except for a mild hypertension of 155/90. Pelvic examination revealed well-developed normal external genitalia. There was no clinical evidence of leucoplakia. Involving the left labium majus and part of the left labium minus was an ulcerated lesion about 4 by 6 cm., with a raised, pearly, hard border (Fig. 4). The base of

the ulcerated lesion was clean and showed no evidence of necrosis. The ulcer was not attached to the underlying tissue, and there did not seem to be any involvement of the adjacent skin. There were some small lymph glands palpable in the left groin. The left leg showed a marked dermatitis and scaling. There were many small varicosities in both lower extremities. A biopsy taken on Jan. 24, 1941, showed a basal cell carcinoma of the vulva. In view of the primary lesion and the palpable inguinal glands, a complete left vulvectomy was done with the cautery, and a left-sided Basset operation was done. The external iliac and obturator glands were found to be definitely enlarged and many small glands were found in the fat

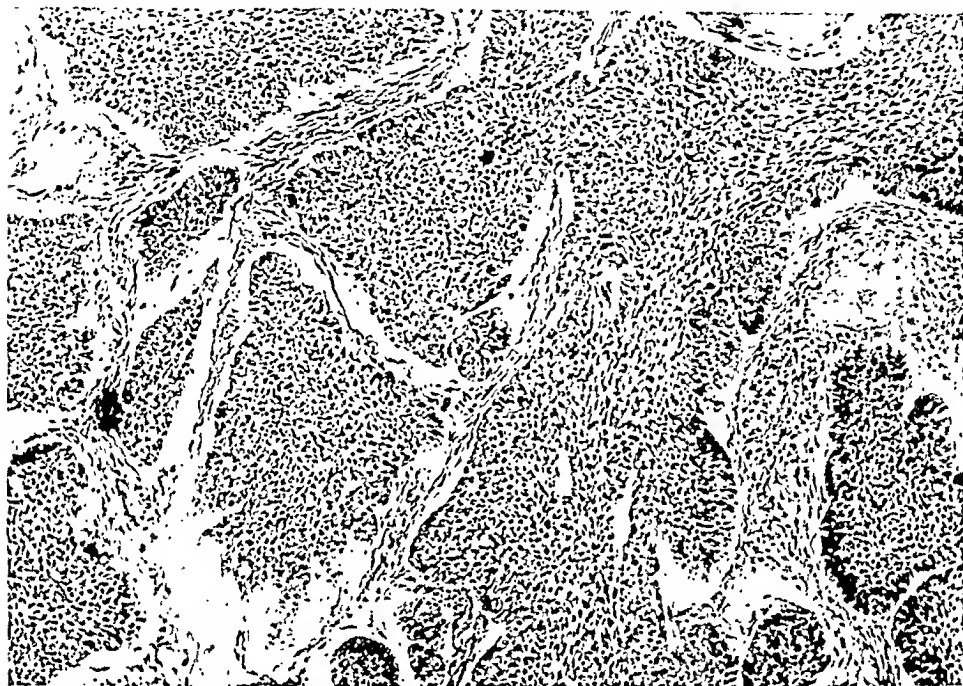


Fig. 5.—Microscopic picture of the lesion in Fig. 4, showing nests of malignant basal cells in a stroma of connective tissue.

in Scarpa's triangle. Microscopically the primary lesions showed nests of epithelial cells of typical basal cell type. These nests of cells were embedded in a dense connective tissue (Fig. 5). The lymph glands showed no sign of metastases. On the eighteenth postoperative day, the primary vulvar defect was skin grafted with pinch grafts and the patient was discharged from the hospital on the twenty-seventh postoperative day.

#### DISCUSSION

In general, these four cases represent the typical history of basal cell carcinoma. The history of a slow, painless growth, with recurrent episodes of ulceration and bleeding, terminating in an ulcerative lesion of varying size and involvement, is one common to basal cell carcinomas anywhere in the body. The absence of metastases in the regional lymph nodes is also a characteristic finding in these cases. These carcinomas are locally malignant and grow by extension, but they hardly ever metastasize. The enlargement of lymph nodes tributary to a basal cell carcinoma is usually due to secondary infection of the primary lesion, resulting in a hyperplasia of the lymph nodes. The follicles become hyperplastic and may be mistaken for areas of metastatic squamous cell carcinoma.



Each of these four cases presents the histologic picture of a basal cell carcinoma. The cells are derived from the basal layer of the epidermis. The cells stain darkly and the nucleus occupies the major portion of the cell, there being relatively little cytoplasm. In Fig. 2, one can see the basal layer of cells undergoing malignant degeneration at the margin of a rodent ulcer. These islets of cells are found in the dermis, and they do not invade the subcutaneous tissue. The other cases show more areas of more advanced malignant change. There is a total absence of keratinization and epithelial pearl formation in these cases. Fig. 3 shows evidence of cystic degeneration in the center of these nests of cells. Mitotic figures are found infrequently in these microscopic sections. These groups of cells do not show invasive tendencies.

Blair Bell and Datnow<sup>1</sup> found that malignant disease of the vulva occurs as squamous cell carcinoma in over 90 per cent of all cases. The other 10 per cent or less includes adenocarcinoma (Bartholin gland), sweat gland adenomas, basal cell carcinoma, melanoma, teratoma, sarcoma and endothelioma. In his analysis of 155 cases of vulvar carcinoma, Taussig<sup>2</sup> found 3 cases of melanoma originating about the labia and urethral meatus, 12 cases of periurethral cancer, 3 adenocarcinomas arising from Bartholin's gland, and the remaining carcinomas were of the squamous cell type. D. den Hoed<sup>3</sup> in analyzing the results obtained with the treatment of malignant tumors of the vagina, vulva, and urethra, found one case of basal cell carcinoma among 41 vulvar tumors, which gives an incidence of 2.5 per cent in this series. Göbel and Hamann<sup>4</sup> collected 69 cases of carcinoma of the vulva between 1915 and 1936. They found that vulvar carcinoma forms 3.5 per cent of all pelvic carcinomas in women. Of these 69 treated patients, 8 cases had recurrences. Among the remaining 61 cases, there were 9 cases of basal cell carcinoma and 44 cases of squamous cell carcinoma. This gives an incidence of 13 per cent basal cell carcinoma in this group. These investigators make note of the fact that the incidence of basal cell carcinoma in their series is higher than any other obtained in the five years previous to their report. Mosto and Radice,<sup>5</sup> reporting 23 primary malignant tumors of the vulva, found 21 carcinomas and 2 tumors of connective tissue origin. Of the 21 malignancies, one was glandular in origin, 19 were spinocellular in type, and one was a basal cell carcinoma. Folsome<sup>6</sup> found that basal cell carcinoma of the vulva is relatively rare. He reports 6 cases from the Michigan University Hospitals. Three patients had rodent ulcers elsewhere on the body, and in 2 cases there was more than one rodent ulcer on the vulva. These were treated by surgical extirpation. Claiborn and Holsinger<sup>7</sup> reported only 2 cases from the literature, and added one of their own.

In his monograph on diseases of the vulva, Taussig<sup>8</sup> divides carcinoma of the vulva into 3 groups:

1. Squamous cell carcinoma or canceroid, characterized by the formation of numerous epithelial pearls.
2. Medullary carcinoma springing from undifferentiated epithelial cells.
3. Adenocarcinomas arising from glandular structures about the external genitals.



He states that in point of frequency, the typical squamous cell cancers predominate and that outside of Bartholin's gland, adenocarcinoma of the vulva has hardly ever been recorded. No mention is made in this classification of basal cell carcinoma.

From a study of these 4 cases, it would seem that the treatment of basal cell carcinoma of the vulva need not be as radical as that of squamous cell carcinoma. A biopsy should be taken in all cases both from the edge and from the base of the ulcer to determine the histologic classification of the neoplasm. If the growth is basal cell in character, then a simple wide excision should be carried out without any extensive glandular removal. The Basset operation is not essential in all cases of basal cell carcinoma of the vulva. However, the patient should be observed every four to six months, and, if at any time a diagnosis of metastases to the regional lymph nodes is warranted, the Basset operation could be done with a reasonable chance of cure. Since none of these cases could be explained on a leucoplakic basis, it was not necessary to do a complete radical vulvectomy in each case. The dissection of the vulvar lesion should be carried down to the superficial fascia, since there is usually no involvement below the subcutaneous tissue. Radiation was not used in any of our cases.

#### SUMMARY

Four cases of basal cell carcinoma of the vulva are presented with case histories and treatment. One death is recorded due to postoperative cardiac failure and pulmonary edema following a Basset operation two years after the preliminary vulvectomy. At the time of the gland removal there was no evidence of any local recurrence. The other 3 patients are alive and well, eight years, nine years, and six months, respectively. All were treated by surgical extirpation without radiation. Three patients had a regional lymph gland removal, but in no case was there any evidence of any metastasis.

#### REFERENCES

- (1) Blair Bell, W., and Datnow, Wm. M.: J. Obst. & Gynec. Brit. Emp. 43: 755, 1936.
- (2) Taussig, F. J.: AM. J. OBST. & GYNEC. 40: 764, 1940.
- (3) den Hoed, D.: Acta Radiol. 17: 569, 1936.
- (4) Göbel, H., and Hamann, A.: Zentralbl. f. Gynäk. 61: 1394, 1937.
- (5) Mosto, D., and Radice, J. C.: Rev. med. y cien. afines 1: 33, 1930.
- (6) Folsome, Claire: J. A. M. A. 114: 1499, 1940.
- (7) Claiborn, Louie N., and Holsinger, Hubert B.: Surg., Gynec. & Obst. 54: 836, 1932.
- (8) Taussig, F. J.: Diseases of the Vulva, New York, 1923, D. Appleton-Century Company.

TABLE III. HYPOPROTEINEMIA FOUND ON FIRST CLINIC VISIT OF PATIENTS WHO BECAME TOXIC

Month of pregnancy	2	3	4	5	6	7	8	9
Number of normal patients studied for protein	20	21	48	60	47	51	36	43
Percentage of normal patients with low protein	20	14.2	12.5	3.3	19.1	13.7	19.4	18.6
Average protein for normal patients	6.9	7.1	6.8	6.9	6.6	6.7	6.7	6.8
Number of toxic patients studied for protein		13	25	31	22	14	7	8
Percentage of toxic patients with low protein		8.3	28.3	29.0	26.3	21.0	42.8	62.5
Average protein for toxic patients (first clinic visit)		7.4	6.4	6.6	6.7	6.5	6.1	5.8

Women with low protein in both the second and third trimesters of pregnancy were much more common among the toxic cases than among the normal ones, while women with low protein in either trimester alone were as likely to belong to one group as the other.

TABLE IV. PROLONGED HYPOPROTEINEMIA AND TOXEMIA

	NORMALS (27)	TOXICS (19)
Number with low protein in both second and third trimesters	1	8
Low in second trimester only	3	3
Low in third trimester only	12	7
Normal protein throughout	11	1

Those whose protein had remained normal throughout pregnancy did not become toxic, with one very mild case excepted, but some whose protein was low remained normal. If the protein is below 5.6 mg. on only one occasion, the patient is not nearly so likely to be toxic later as is the woman whose protein values have averaged 6.0 Gm. or less.

TABLE V. SIGNIFICANCE OF OCCASIONAL HYPOPROTEINEMIA

	NORMALS (27)	TOXICS (19)
Normal protein throughout	11	1
Low protein on any occasion	16	18
$\chi^2$ is 7.27		P is less than 0.01

TABLE VI. SIGNIFICANCE OF LOW PROTEIN AVERAGE

	NORMALS (27)	TOXICS (19)
Normal protein average	18	4
Low protein average	9	15
$\chi^2$ is 9.23		P is less than 0.0

Among the patients who were hospitalized for toxemia, there were some who were less toxic than others. The figures from all patients hospitalized appear in Table VII.

Nearly all of the patients hospitalized had low protein. The a/g ratio was not under one (or inverted) except in two cases (9 per cent), but it was often decreased toward one. According to the fall of the a/g ratio value in proportion to the decrease in total protein, the patients could be divided into three groups. In the largest group, the fall of total protein was great but the ratio remained nearly normal. In the second group, almost equally large, the fall in both values was

delivered normally. No tears of any kind were observed. Pituitrin, 0.5 c.c., was injected intramuscularly and the intact placenta came away spontaneously. There was no hemorrhage. Ten minutes after the extrusion of the placenta, the patient complained of a chill and seemed to go into a mild shock. This was believed to be due to the pituitrin and external heat was applied. At 10:10 (thirty-five minutes after the placenta was expressed), the patient complained of a severe "pressing and shooting" pain in the region of the coccyx and in the right buttock. There was a bulging in the right vulvovaginal wall and during the examination, this bulge gave way. The patient stated that she felt something give way but that she now felt all right. She was given  $\frac{1}{8}$  gr. of morphine subcutaneously. At 11:00 P.M. (fifty minutes later), she suddenly shrieked and stated that the pain returned, was more intense,

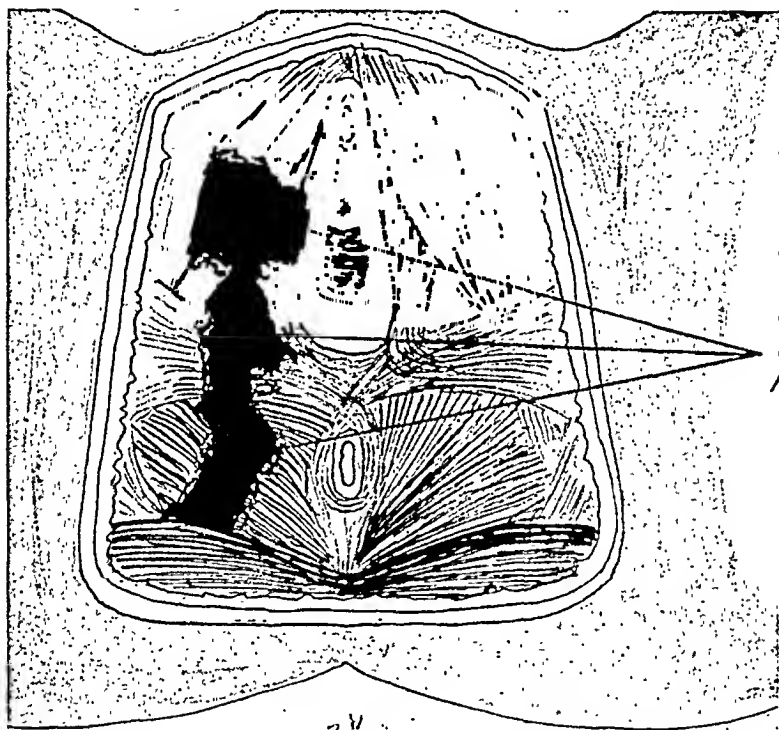


Fig. 1.—Semi-diagrammatic representation of rupture of all the muscles in the right perineum with the exception of the gluteus maximus. Note extent of rupture and hemorrhage, indicated by lines.

and that now, in addition, she had pain in the vagina. At this time, examination revealed the patient in shock and symptoms of an internal hemorrhage were present, i.e., anemia, restlessness, air hunger, rapid thready pulse of 140, numbness and coldness of the extremities, etc. There was a globular mass about the size of a large grapefruit in the right vaginal wall which was fluctuant, tense, purplish, and elastic. The mass was tender and the vaginal wall was glistening. Any movement of the right hip was excruciatingly painful. The fundus was firm, and there was no bleeding from the cervix.

Immediate surgery was done. When a longitudinal incision of the right vaginal wall was done, 1,500 to 1,800 c.c. of bright red blood and clots were evacuated. Hemorrhage was brisk. Hot packs were applied and bleeding points were ligated. After active bleeding was controlled,

## HEMATOMA OF THE VAGINA ASSOCIATED WITH SEVERE PERINEAL TEARS

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**V**ULVOVAGINAL hematoma is, in itself, a rare condition, but, combined with a complete rupture, unilaterally, of all the muscles of the pelvic floor with the exception of the gluteus maximus without a tear of the vaginal wall, has not, so far as the literature is available, been reported previously.

Mrs. E. B., aged 20 years, white (married to an Indian), para i, gravida ii, presented herself on March 7, 1940, for a prenatal examination. Her past history was essentially negative except for chicken pox at 6 years of age. The menstrual history was normal; menses began at 14, were regular, every twenty-eight to thirty days, lasting four days with little or no associated pain, and a moderate amount of discharge. There was occasionally a small amount of leucorrhea between periods. Venereal disease was denied. Her first child was born three years previously in an apparently normal delivery after a labor of fourteen hours. She was told by her physician that she suffered no tears and her postpartum course was smooth and uneventful.

Examination at this time revealed a well-developed, slender white woman, 62 inches tall (157.5 cm.), weighing 104 pounds (47.3 kg.), in good health, with a blood pressure of 118/70 mm. Pelvic measurements were a bitrochanteric distance of 32 cm., Beaudelocque's diameter of 19.5 cm., conjugate vera 11.0 cm., bispinous distance 11.0 cm., and a biischial diameter of 11.5 cm. The cervix was normal and pointed anteriorly. Hegar's sign was present and the uterus was 3 fingers above the symphysis pubis. The patient reported once monthly and the pregnancy progressed satisfactorily. In May, the patient had a thrush of the vagina which promptly cleared up after two treatments of soap and water scrubs, followed by application of a solution of gentian violet. She had a recurrence of moniliasis in July, 1940, which similarly responded to treatment. Urinalysis on all occasions presented normal findings. Her blood picture on July 2 was red blood count 4,750,800; hemoglobin (Sahli) 92 per cent; white blood count 7,300, of which 68 per cent were polymorphonuclear leucocytes, 22 per cent small lymphocytes, and 10 per cent large lymphocytes. Wassermann, Kahn, and Mantoux reactions were all negative.

On October 1, the patient reported for her last examination prior to delivery and stated she felt lightening two weeks previously. Nothing abnormal was found at this time. She entered the Holy Family Hospital on October 10 because of some irregular "labor pains." On October 11, at 5:00 P.M., she began to have pains fifteen minutes apart, lasting fifteen to twenty seconds. The pains increased in severity and intensity until about 8:00 P.M. when, upon examination, the cervix was completely dilated, the baby in R.O.A., and head deeply engaged. At 9:25 P.M., a living female child, weighing 7 pounds (3,180 Gm.), was

hematoma was sufficient to do this. It will be observed that the clitoris and rectum were uninjured. This was presumably due to the fact that the hemorrhage did not ramify and burrow in those directions. Furthermore, these structures could easily be pushed out of the way by the mass of blood. The peritoneum was also untouched. It is likely that this may be due to the fact that the peritoneum is elastic, can stand much stretching and there are no relatively inelastic attachments. The gluteus maximus is too strong a structure to be torn in this manner.

#### SUMMARY

1. A case is presented of a vulvovaginal hematoma with severe internal perineal tears.
2. There was no apparent etiology for these conditions inasmuch as the delivery was normal, there were no apparent blood dyscrasias, labor was not prolonged, the baby was normal in size and weight, and there were no convulsive or violent movements during delivery.
3. There was an immediate hematoma followed by a latent period and finally true hematoma and tears.
4. Surgery was instituted on diagnosis with complete recovery.
5. A brief discussion of etiologic and surgical factors is presented.

## DERMOID CYST IN THE UTERINE TUBE

### A CASE REPORT WITH A REVIEW OF THE LITERATURE

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ONLY twenty-four dermoid tumors of the uterine tube have been recorded; it, therefore, seems worth while to report an additional case. Only 4 of these are recorded in English, therefore the most salient features of all cases will be reported. It was not possible to obtain the report of Müller's case. Those of Prochowniek and Ostreil are incompletely described. It is questionable whether the tumor described by Roberts is primarily tubal in origin. Previous authors have referred to the case reported by Robert Meyer; however, this is quite definitely a dermoid cyst of the ovary which encroached upon the uterine tube.

#### CASE REPORT

The patient, 33-year-old unmarried clerical worker, was admitted to the Beth Israel Hospital because of profuse vaginal bleeding (myomatous uterus). A supraervical hysterectomy and left salpingo-oophorectomy were performed. On gross examination the uterus, except for several large and small myomas, showed nothing unusual. The left ovary contained two corpora lutea. The tube was thin and slightly tortuous. Its fimbriated extremity was patent. Several pinhead-sized and larger thin-walled, clear cysts were situated on its posterior surface and in the broad ligament. At a distance of about 5 cm. from the tubal angle the tube was swollen, reaching a diameter of 1.5 cm., the tube then gradually tapering to normal thickness, which was reached about 3 cm. from the abdominal ostium. In the swollen area the whole thickness of the

torn muscle and fascia were observed in the cavity. The m. ischio-cavernosus, the m. bulbocavernosus, the m. transversus perinei, and the m. levator ani were ruptured. The edges were ragged and thinned out. The sphincter ani and the m. gluteus maximus, the peritoneum, the urethra and the clitoris were intact. The vaginal wall, except for some thinning, appeared to be normal. Repair of the torn muscles and fascia was accomplished by mattress sutures with No. 0 twenty-day chromic gut after freshening and trimming the edges. The vaginal wall was sutured with No. 00 chromic and the expected cystocele was prophylactically corrected by a modified Graves operation for cystocele. An indwelling catheter was inserted and dry pads applied. Shock and blood loss were appropriately treated.

The postoperative course was uneventful except for a severe secondary anemia.

Blood counts were as follows:

10/16/40	red blood count	2,620,000 Hg (Sahli)	34%
10/20/40	red blood count	2,760,000 Hg (Sahli)	29%
10/23/40	red blood count	3,030,000 Hg (Sahli)	32%
10/26/40	red blood count	2,900,000 Hg (Sahli)	32%

The catheter was removed on the second day postoperatively, and the patient left the hospital sixteen days later.

Weekly follow-ups were done, and no evidence of searring, cystocele, or rectocele was noted. Until the middle of November, there was some pain on defecation and on walking. The pain was localized in the right perineum and groin. But this too disappeared. On Nov. 14, 1940, the red blood corpuscles were 4,130,000 per c. mm.; hemoglobin 61 per cent. On Dec. 18, 1940, the red blood corpuscles were 4,690,000 and hemoglobin 96 per cent.

The patient, at the present writing, shows no abnormal external findings, but on deep palpation vaginally, an occasional mildly tender area may be demonstrated. There is no evidence of rectocele or cystocele. She has normal sexual relations and subjectively feels "better than ever."

#### COMMENT

It is interesting to note that a vulvovaginal hematoma developed a few minutes post partum. This hematoma, before and during examination, probably burrowed along fascial planes and the sensation of something giving way was due to rupture either of some of the perineal muscles or of fascia which may have been caused by purely mechanical pressure transmitted through the fluid contents of the hematoma. However, the manipulation during the examination was gentle and a more likely hypothesis would be that the hematoma burrowed through the fascial planes, separating and dissecting them from their normal close relationship. Moreover, while this hematoma was becoming progressively larger, ragged tears, thinning of muscle due to pressure of the increasing globular mass, and finally rupture of the fascial sheaths and muscle tissue ensued. After the initial rupture of portions of the muscles, these tears were further enlarged not only by the hematoma but by additional blood from the torn structures. During the process, there was a period free from pain but the recurrence of the pain occurred probably at the time when rupture of a partially torn muscle was completed. A great force is not necessary to tear muscles even as large as the levator ani, and probably the pressure exerted by a rapidly forming

TABLE I. RECORDED CASES OF TUBAL DERMOID CYSTS

AUTHOR	DATE	AGE	GRAV.	HISTORY	SITE	SIZE	LOCATION	CONTENTS	
Eden and Lockyer	1865			Not given		Large cocoon	Luminal, with a pedicle	Solid, with skin, sebaceous glands, hair, fibrous tissue, and areolar tissue	
Scott	1883	55	iv	Protruded uterus 25 years. Menopause, 4 yr. Painful mass on right	Right	4 pounds	External. The tube formed the pedicle	Contained cheese, hair, and bone	
Schouwmann	1890	43	xi	Pain in the R.L.Q. for 4 months	Right	Egg	In the lumen	Cystic, containing fat and hair	
Pozzi	1896	33½	ii	Pain on left. Puerperal infection, 7 mo. Pregnancy in other tube	Left	----	In the lumen	Cystic, with cornified skin, sebaceous glands, sweat glands, hair, and adipose tissue	
Jacobs	1899	48	0	Irreg. painful menses, 3 years. Painful mass on the left	Left	Orange	Outer third of the tube	Cystic, with sebaceous and calcareous matter. Author states microscopies showed exclusively dermoid of tube	
Noto	1900	25	0	4 year history of painful enlarging tumor	Right	Orange	In the lumen	Cystic, containing tallow epithelium, sebaceous glands, endothelium, and round cells	
Roberts Questionable case	1903	29	0	Amenorrhœa, 4 months. Ruptured tubal pregnancy, right	Left	1¼ × ¾ in.	Attached to the fimbriated end	Solid, containing bone, cartilage connective tissue and epithelial necrotic mass.	
Orthmann	1904	33	ii	Meno- and metrorrhagia. Pain in the R.L.Q. Pelvic adhesions	Right	9 × 3 × 4cm.	Attached to inside of tube by a thin pedicle	Cystic, with skin, hair, sebaceous and sweat glands, areolar tissue, smooth muscle, cartilage, bone, nervous tissue, giant cells, endothelium	
Prochowick	1905		Not given			Presentation of gross specimen. Both ovaries normal.			No description found

tube appeared to be replaced by a unilocular cyst. The contents of the cyst after fixation were light grayish and gelatinous. No hairs were seen. The cyst wall easily separated into three layers, the middle of which was less than 1 mm. thick. The inside of the cyst was mostly smooth with some more or less distinct pits, grooves, and ridges. There was no communication on either side between the tube lumen and the cyst cavity. Cross sections of the tube on both sides of the cyst revealed nothing unusual.

*Microscopic Examination.*—Cross sections through the tube away from the swelling and long sections through the edges of the swelling did not reveal any abnormality or inflammation in the tube. The tube wall, especially the folds, was simply thinned out where it had been subjected to the pressure from the cyst. The thin-walled sac which fell out when the specimen was opened was lined with epithelium on its inner

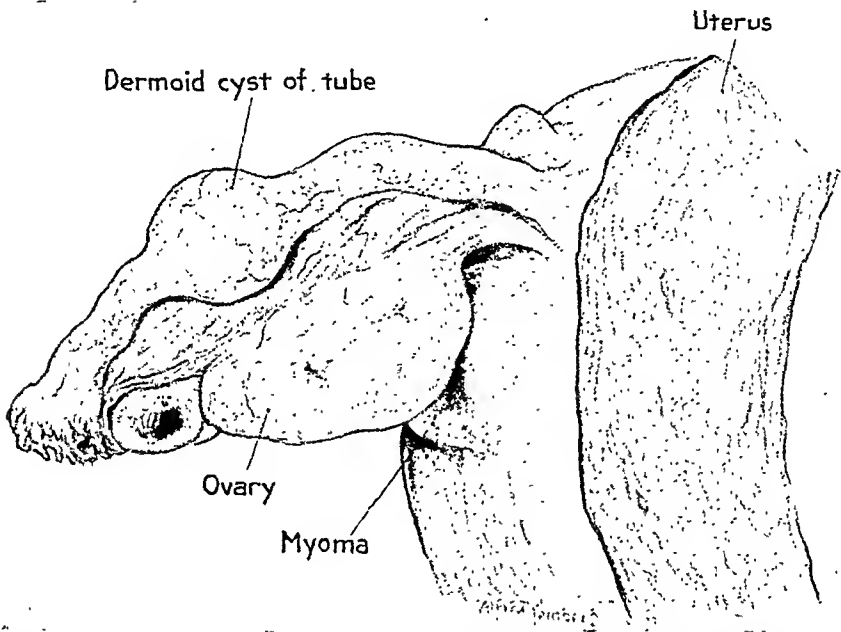


Fig. 1.—Gross specimen of tube and ovary. The swelling in the midportion of tube which represents the dermoid cyst has been bisected. The cyst at the lower edge is a large serosa cyst.

and its outer circumference. There were some folds and grooves. The epithelium at the outer circumference resembled tubal epithelium. It consisted of one layer, the cells were mostly cylindrical, many were cuboidal or flat. Cilia were seen occasionally on small groups of the cylindrical cells. There was little secretion. The inner epithelial lining was multilayered, ciliated throughout. There were occasional mucinous cells. The surface was smooth, only one fold was seen in the whole section. The stroma between these two layers was edematous. It consisted of connective tissue mostly, lymphoid foci (without centers), small and large areas of hyaline cartilage, nervous tissue, ganglion cells, and glands of bronchial type. Some of these glands had widely distended ducts. These small cysts were lined with flat epithelium, some of them empty, some filled with homogeneous material. In some sections the thin wall of the dermoid cyst could be studied in situ but no connection between tubal folds and the cyst wall could be found.



TABLE I—CONT'D

AUTHOR	DATE	AGE	GRAV.	HISTORY	SITE	SIZE	LOCATION	CONTENTS
Aleev and Mamenkov	1925	48	iii	Abdominal pain for nine years	Right	Child's head	External. Attached to tube wall by a pedicle	Cystic with hair, balls, epithelium, sweat glands, Leiberkühn glands, intestinal lymph follicles, pancreas, cartilage, areolar tissue, thyroid, bone, and respiratory epithelium
Ronsisvalle	1927	46	0	Dysmenorrhea. Menorrhagia. Epigastric mass.	Bilateral	Lemon	In the lumen. The entire tube involved	Cystic, with pap, hair, skin, connective tissue, smooth muscle, areolar tissue, round cells, sieve-like areas, simple tubular glands
Neumann	1927	36	i	Right tubal pregnancy mass on left side	Left	3.4 × 1 cm.	Attached by a pedicle to the inner wall of the tube	Cystic, with skin, sebaceous and sweat glands, fat and connective tissue, gland ducts lined with cylindric epithelium, round cells, giant cells
Aschheim	1932	42	0	Ovarian tumors, 4 years	Left	Finger	Attached by a pedicle to the inner wall of the tube	Solid, with skin, gland-like spaces lined with cylindric epithelium, mucous epithelium, cartilage, smooth muscle, adipose tissue, and round cells
Kraul	1938	40	-	Not given	Right	Child's head	External, with a pedicle	Solid, with skin, hair, smooth muscle, bone, cartilage, and connective tissue
Müller	1938	Not given	Not given	L. tubo-ovarian dermoid cyst. R. ovarian dermoid cyst	Right	Not given	Ampullary portion	Case details cannot be obtained
Aaron	1941	33	0	Meno- and metrorrhagia	Left	1.5 × 1.5 cm.	Intramural outer third of tube	Cystic, with skin, bronchial epithelium, cartilage, smooth muscle, nerve tissue, and round cells

Sneguireff	1905	-	(Twins) xiv	Dysmenorrhea. Palpable abdominal tumor	Right	---	In the lumen	Cystic, with epithelium, islands of cartilage, and glands
Potherat	1907	37	0	Pelvic adhesions	Bilateral	R—Orange L—Tangerine	In the lumen	No further description given
Stark	1912	38	0	Sterility. Dysmenorrhea	Bilateral	Tangerines	In the lumen	Cystic, with sebaceous matter, hairs, and plates of bone
Muglich	1912	Not given	Not given	Myoma uteri. Dysuria	Not given	---	Attached by a pedicle to the inner tube wall	Cystic, with greasy material and an "Embryonkörper,"
Ostreil	1913	Not given	Not given	Not given	Not given	Not given	----	Cystic, with hair and nervous tissue
Orthmann	1914	45	ii	Prolapsed uterus	Right	Hazelnut	In the lumen attached by a pedicle to the inner tube wall	Cystic, with derivatives of all three germinal layers
Ohno and Takaoka	1918	36	i	Pain, leucorrhea. Abdominal fullness for 10 yr.	Right	(cm.) 6.5 x 5.7 x 4.5	In the lumen. Isthmic portion of the tube	Cystic with pap, epithelium, hair, sebaceous and sweat glands, areolar tissue, cartilage, bone, nerve tissue, intestinal mucosa, giant cells, and smooth muscle and esophageal mucous membrane
Delannoy	1923	32	0	Fever and abdominal pain for 7 years. Bilateral pelvic tumors	Bilateral	R.15.5 x 13 x 12 cm. 470 Gm. L.15 x 5.5 x 5.5 cm. 275 Gm.	In the lumen. Outer third. Abdominal end	Cystic, with cartilage, bone smooth muscle, and sebaceous glands. Cystic, with 3 coats, desquamating pavement epithelium, cuboidal cells, sebaceous glands
Ulesko-Stroganova	1925	Not given	0	Sterility. Meno- and metrorrhagia	Right	Egg	Attached to cornu by a pedicle formed by tube and ligament	Cystic, with skin, hair, bone, sebaceous glands, fat, giant cells and sieve-like areas

Gynäk. 53: 119, 1904. *Prochownik*: München. med. Wehnschr. p. 1312, 1905. *Sneguireff*: Ann. de gynéc. 32: 265, 1905. *Meyer*: Zentralbl. f. Gynäk. 46: 1, 1905. *Potherat*: Bull. et mem. Soc. Chir. de Paris 33: 657, 1907. *Stark*: J. Obst. & Gynaec. Brit. Emp. 22: 217, 1912. *Ostrel*: Zentralbl. f. Gynäk. 37: 755, 1913. *Orthmann*: Ztschr. f. Geburtsh. u. Gynäk. 76: 621, 1914. *Muglich*: Monatschr. f. Geburtsh. u. Gynäk. 35: 105, 1918. *Ohno and Takaoka*: Gann 12: 24, 1918. *Delannoy*: Gynec. et obst. 7: 301, 1923. *Ulesko-Stroganowa*: Arch. f. Gynäk. 123: 175, 1924. *Aleev and Mamcnkov*: Kazan M. J. 21: 835, 1925. *Ronsisvalle*: Riv. ital. di ginec. 9: 422, 1927. *Neumann*: Arch. f. Gynäk. 130: 766, 1927. *Aschheim*: Ztschr. f. Geburtsh. u. Gynäk. 103: 652, 1932. *Müller*: Casop. lék. česk. 77: 1, 1938. *Kraul*: Zentralbl. f. Gynäk. 62: 2113, 1938.

## BICORNUATE UTERUS, FULL-TERM PREGNANCY, AND PREMATURE SEPARATION OF CENTRAL PLACENTA PREVIA

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(From the Obstetrics Service of the Los Angeles County General Hospital)

THIS patient presents a checkered obstetric history, including several pathologic labors and deliveries, in which a premature separation of a central placenta previa took place in a bicornuate uterus containing a full-term living baby in one horn.

The literature contains numerous reports of full-term pregnancies in double uteri; most of these are found in foreign publications and describe single cases. Frequently, the pregnancies terminated spontaneously with living babies. Beaver and Abbott<sup>1</sup> discuss normal pregnancies and deliveries in bicornuate uteri, with an extensive review of the literature. They collected numerous cases in which the pregnancy went to term. Falls<sup>2</sup> has frequently stressed the abnormal physiology of the uterus arcuatus.

In the patient herein described, the bicornuate uterus seems to have been an incidental occurrence which in no way hindered an extensive obstetric experience; however, its presence may have contributed to the existence of several pathologic labors and deliveries.

### CASE REPORT

C. G., a 28-year-old Mexican female (Hospital No. 318533), entered the Los Angeles County General Hospital on Feb. 26, 1941, at 10 P.M. She stated that her pregnancy, now in the eighth month, had been entirely uneventful until the afternoon of admission, when she noticed slight bleeding followed by cramping pains.

Examination revealed an obese woman in good physical condition except for a blood pressure of 160/100. She had attended a suburban clinic for "chest trouble and bronchitis" for the preceding year, but a lung roentgenogram was negative. The blood and urine were negative.

Sterile vaginal palpation demonstrated an elongated cervix admitting a finger, moderate bleeding, and definite placental tissue directly over the internal os. Bleeding recurred after examination. The cervix and vagina were packed tightly with small moist cotton pledgets. This checked the bleeding.

## COMMENT

It is beyond the scope of this paper to present the numerous theories concerning the genesis of teratomatous tumors and dermoid cysts. However, from a study of the recorded cases, as well as of our own, it is felt that the mode of development of these growths in the uterine tube may be demonstrated. As the Müllerian grooves in the urogenital fold become differentiated into the Müllerian ducts, a blastomere may become misplaced in the coelomic epithelium and is then incorporated in the tube wall to develop subsequently into a dermoid cyst or solid teratoma. It may reach intramural or grow inwards and perforate, or be attached by a pedicle to the inner wall of the tube; or else it may grow outward. Of the 23 adequately described cases the tumors were luminal in 15, of which 5 were pedunculated, 2 mural, and 8 external with a pedicle. Generally, the appearance was that of sactosalpinges, usually with adhesions to adjacent structures. In practically every instance the growths were situated in the middle or outer third of the tube. The cystic form is by far the commonest, in the ratio 20:6. No instance of malignancy is reported in the solid teratomas. Hairs were present in 12 cases. Their size varied from that of a hazelnut to a child's head. Since all the growths were incidental findings during the course of a gynecologic operation, statistics as to their frequency with respect to age are of little value. They have been found in patients from 25 to 55 years of age; 9 of these were parous, and 9 were nulliparous. In 3 cases there was a pregnancy in the opposite tube. They were more commonly unilateral than bilateral, in the ratio of 16:5, and occurred on the right side in ten instances, and on the left in six. It is interesting to note in this connection that dermoid cysts of the ovary seem to occur with equal frequency on either side, while teratomas of the testicle occur more frequently on the right. From the little material available at present, however, no conclusion may be drawn.

It is not easy to reconstruct in one's mind the arrangement and the way of formation of this dermoid in the tube. The thin sac which fell out when the swelling was incised consists of dermoid tissue and of tubal fold tissue. A similar layer, however, remained on the inside of the thinned-out tube wall after the aforementioned sac had been removed. We might assume that the dermoid cyst developed within a tubal fold replacing most of the tubal fold tissue by dermoid structures. While part of the dermoid formed a thin-walled round cyst, other parts infiltrated adjacent portions of tubal folds. Judging from the extreme thinning out of the tubal folds in the dermoid and in its neighborhood, it is not too difficult to conceive that one or several folds were completely destroyed by pressure atrophy, for instance, thus explaining the fact that one part of the dermoid was completely separated from the remainder.

## SUMMARY

A case of a dermoid cyst in the uterine tube is presented. The dermoid obviously originated within the tubal mucosa.

## REFERENCES

- Eden and Lockyer*: New System of Gynecology 2: 736, 1865. *Scott, John*: Pacific M. & S. J. 26: 401, 1883. *Schouwmann*: Nederl. Tijdschr. v. verlosk. en gynaec. 2: 235, 1890. *Pozzi*: Traite de Gyn. Clin. et Operatoire, ed. 3, 1896, p. 866. *Jacobs*: Bull. Soc. belge de Gynaec. 10: 20, 1899. *Noto*: Arch. ital. di ginec. p. 291, 1900. *Roberts*: Lancet 24: 1165, 1903. *Orthmann*: Ztschr. f. Geburtsh. u.

TABLE VII. DATA ON PATIENTS HOSPITALIZED FOR TOXEMIA

INITIALS	PROTEIN	ALBUMIN	GLOBULIN	A/G RATIO	HEMOGLOBIN	INTERVAL BEFORE OR AFTER	BLOOD PRESSURE AND OTHER DATA
1 J. M.	5.2* 7.4	2.1 2.5	3.1 4.5	0.7 0.5	9.0	23 days after	200/124, eclampsia, hepatomegaly, positive Takata-Ara test
2 D. T.	7.8 5.9*	3.7	2.2	1.7	11.6	90 days before	Eclampsia Dead child
3 B. S.	6.3 4.4*				13.4	90 days before	Post-partum convulsions Excessive weight gain
4 W. S.	7.7 6.0* 6.4	3.4 4.0	2.6 2.4	1.3 1.7	10.4	70 days before 70 days after	Pre-eclampsia, 157/60 Excessive weight gain
5 C. McD.	6.5 6.0*	3.7	2.3	1.6	10.0	60 days before	Severe pre-eclampsia, 175/110
6 C. S.	9.7 6.3 5.2* 5.8	3.5 3.5 3.3	2.8 1.7 2.5	1.3 2.0 1.3	12.0	90 days before 10 days before 10 days after	180/100
7 B. S.	5.9 4.1* 4.5 4.8 6.9	2.8 3.0 3.1 4.7	1.3 1.5 1.7 2.2	2.1 2.0 1.8 2.1	14.0	100 days before 4 days after 11 days after 18 days after	155/110, albumin 4-plus Edema 2 plus. She had convulsions after previous pregnancy
8 R. W.	8.5 4.6* 5.0 6.9	3.1 2.6 4.0	1.5 2.4 2.9	2.0 1.1 1.4	15.2	105 days before 5 days after 12 days after	170/130, albumin 4-plus, excessive weight gain, edema 1-plus. Blood uric acid 5.0 mg.

A careful obstetric history-taking revealed the following bizarre career:

- 1931 Breech delivery of a living 8-pound baby.
- 1932 Breech delivery of a stillborn 7-pound baby.
- 1933 Spontaneous abortion at 4½ months.
- 1934 Transverse presentation, prolapsed hand, four-hour labor, delivery of a living 6-pound 7-ounce baby.
- 1936 Unattended delivery, one-hour labor, 6-pound baby.
- 1937 Transverse lie, mild pre-eclampsia, Voorhees' bag induction, version and extraction of a living 5-pound 3-ounce baby. The obstetric resident at the Los Angeles County General Hospital made a diagnosis of "double uterus" at this delivery.
- 1938 Spontaneous delivery, cephalic presentation, of 6-pound 8-ounce baby, complicated by unexplicable bleeding. Placenta previa or marginalis was suspected.
- 1939 Spontaneous abortion at 4 months, followed by curettage for postabortal bleeding.

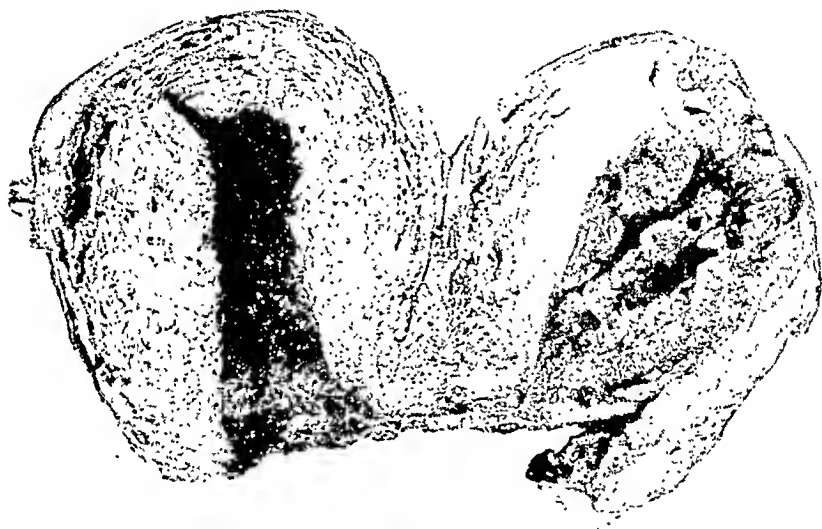


Fig. 1.—Frontal section of bicornuate uterus, showing medial septum and placental site in right horn.

Laparotomy was immediately performed, using spinal anesthesia. The uterus was found to consist of two horns. The fetus occupied the right horn; the left horn was enlarged to the size of a four months' pregnancy. A low cervical incision was made through the uterine muscle transversely, and on exposure of the unruptured membranes, the placenta could be seen floating off its bed over the internal os. The membranes were then incised, the bloody amniotic fluid aspirated, and the fetus was delivered by podalic version. It was a stillborn female consistent in size with an eight months' pregnancy. Acting on the patient's preoperative request, sterilization was accomplished by extending the transverse uterine incision so as to perform a supracervical hysterectomy. She received a transfusion of 500 c.c. of citrated blood and was returned to the ward in good condition. She left the hospital on the eleventh day, after a completely uneventful postoperative course.

The uterus was bicornuate; the larger horn was 13 cm. and the smaller horn 12 cm. from the fundus to the point of amputation, as measured on the postoperative specimen. A thick  $1\frac{1}{2}$  cm. septum separated the two uterine cavities, and there was a common internal os and one cervix (Fig. 1). DeLee<sup>3</sup> calls this anomaly "uterus bicornis unicollis." The placenta was grossly normal, and a large retroplacental clot adhered to its maternal surface. Sections of the tissue showed hypertrophy and hyperplasia of the myometrium characteristic of pregnancy, with decidual endometrium in each horn.

#### SUMMARY

A patient with a history of several pathologic labors and deliveries was delivered by cesarean section of a full-term living infant in one horn of a bicornuate uterus in which there was premature separation of a central placenta previa.

#### REFERENCES

- (1) *Beaver, M. G., and Abbott, K. H.*: California & West. Med. 47: 41, 1937.  
 (2) *Falls, F. H.*: AM. J. OBST. & GYNEC. 38: 661, 1939. (3) *DeLee, J. P.*: Principles and Practice of Obstetrics, ed. 6, Philadelphia, W. B. Saunders Company, p. 561.

### AN UNUSUAL BIRTH INJURY

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MUCH has been written of birth injuries and their management, but a brief survey of the literature and conversations with obstetricians of great experience fail to record a laceration similar to this case.

Mrs. S., nullipara, aged 30 years, was first seen in her second month of pregnancy. Her past history was essentially normal except for the fact that she was an habitual aborter. Examination revealed no abnormalities. Pelvic measurements were normal. Following examination the patient experienced some intermittent uterine contractions and spotting. For three months she was treated with massive doses of lipolutein and vitamin E. The remaining months of her pregnancy were entirely uneventful.

Labor began spontaneously seven days ahead of schedule. The first stage lasted thirteen hours and thirty minutes. Several hours after the onset of labor her pains became weak and irregular. This necessitated the administration of pituitrin, minims 1, 2, and 3, respectively, at thirty-minute intervals. Satisfactory analgesia was obtained with 10.5 gr. of sodium delvinal in divided doses over a nine-hour period. The membranes ruptured spontaneously at the end of the first stage. After forty-five minutes of the second stage, crowning occurred and the patient was then anesthetized with nitrous oxide and ether. The perineum and pelvic floor were "ironed out" and a midline episiotomy was performed; the upper margin of the incision extending approximately one inch above the hymenal ring. Forceps were applied to the head in L.O.A. position. Minimal traction was required for extraction. As the

forehead appeared over the perineum, the child's right hand suddenly protruded up to the elbow through the anus. This was immediately followed by the left hand which protruded up to the level of the wrist. Following delivery of the head and shoulders, the arms were easily drawn through the fistulous opening. With the completion of the third stage, a survey of the damage done revealed no extension of the medial episiotomy. The sphincter ani remained intact, as did the rectal wall for two inches above the anus and three-fourths of an inch above the level of the episiotomy.

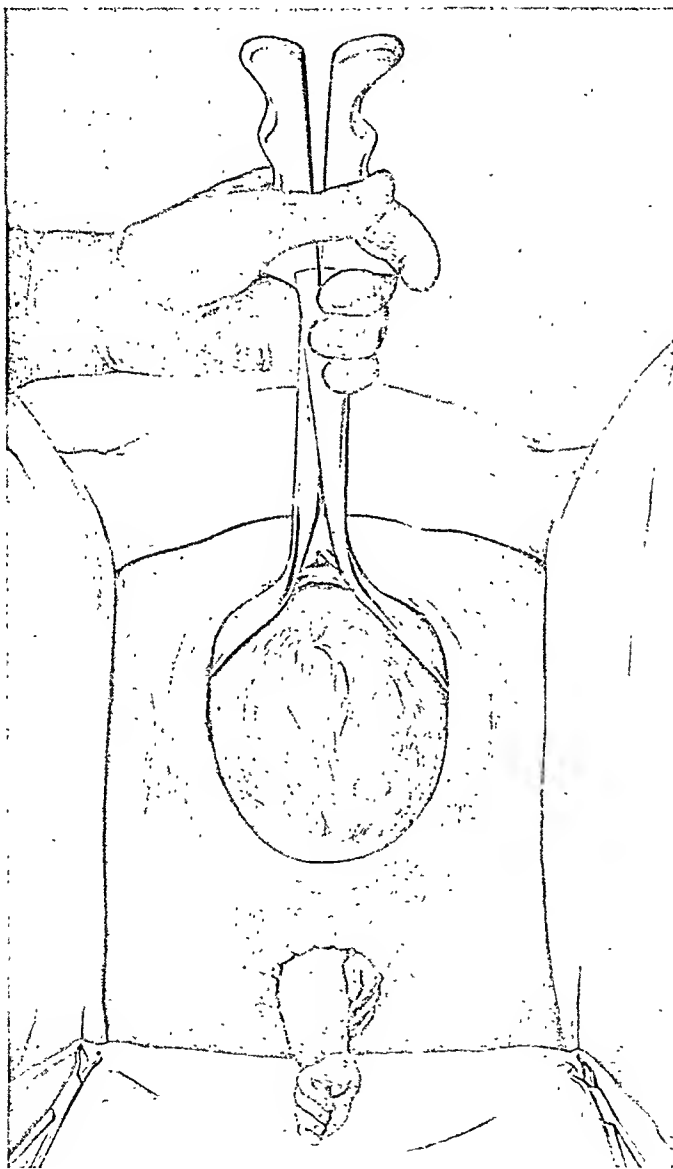


Fig. 1.

A complete laceration was effected by extending the episiotomy through the sphincter and rectal wall and into the fistulous opening. The rectum was closed in two layers; (1) a continuous submucous mattress suture of No. 0 plain catgut and (2) a continuous suture through the rectal muscle wall. The sphincter edges were approximated with



three interrupted 20 day No. 2 chromic gut. The vaginal wall was closed with interrupted No. 1 chromic gut. The perineal muscles were approximated with three interrupted chromic No. 1 sutures and the skin closed with a subcutaneous stitch of No. 1 catgut.

The baby was a healthy boy, weighing 6 pounds and  $3\frac{3}{4}$  ounces. Occipitomenal diameter was 13 cm.; occipitofrontal, 11 cm.; suboccipitofrontal, 10 cm.; suboccipitobregmatic, 9 cm.; biparietal, 8 cm.; bitemporal, 7 cm.; occipitomenal circumference,  $14\frac{1}{2}$  cm.; shoulder diameter,  $5\frac{1}{2}$  inches.

The patient's puerperium was uneventful, and there was no incontinence of feces or gas. She left the hospital on the fifteenth post-partum day in excellent condition. The perineum had healed by primary intention. No extensive examination was made on discharge. Reports from the patient two months after delivery reveal that she retains perfect rectal control and has no perineal distress.

There is no satisfactory explanation for this unusual occurrence. The most logical one is that the attitude of the baby was responsible for the protrusion of the hands through the rectum and that, instead of the arms and hands being flexed across the thorax, the right finger tips were placed over the fetal chin and upon extension of the head the fingers pierced the rectovaginal septum. The left hand was apparently placed alongside the right forearm, as it appeared through the anus shortly after the right arm presented.

In the management of these cases, the major responsibility rests with the nursing staff for the meticulous aftercare so necessary for effective healing. The perineum was kept dry and clean. External antiseptic douches were given after each defecation and urination; the perineum was kept covered with a sterile pad. The perineum was painted with 4 per cent mercurchrome twice daily. No leg exercises were allowed for two weeks. Clear liquids only with no milk products were given for the first five days following which a low residue diet was given for the remainder of the lying-in period. Petrolagar, ounce 1, twice daily was begun on the second day in order to assure free movement of soft fecal matter. Retention enemas of petrolagar and water, ounces  $11\frac{1}{2}$  of each, were given on the third and fourth days. The patient left her bed on the tenth day.

There are two main schools of thought as to the aftercare of third degree lacerations; those who, like myself, believe in opening the bowels early and those who "look them up" for the first week. This latter group believes best results are obtained by putting the intestinal tract at absolute rest, thus allowing time for primary healing. It has been my experience that best results are obtained by keeping the contents of the intestinal tract soft and unformed. Most complete tears are unpredictable and therefore the bowel, as a rule, has not been completely emptied before delivery. If peristalsis has been arrested, the fecal matter becomes dehydrated and presents itself in the form of hard and unyielding masses which, when passed on the seventh or eighth day, are liable to sever all suture lines. With experience in several large maternity hospitals, I have followed at least 25 complete lacerations handled by the above method. All but one case healed by primary union and that one developed a superficial infection which was controlled before the deeper structures were involved, and the patient left the hospital with perfect bowel control. No secondary repairs were required.

# Society Transactions

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## OBSTETRICAL SOCIETY OF BOSTON

*Meeting of October 21, 1941*

The following paper was presented, by invitation:

**The Vital Revolution.** Mr. Guy Irving Burch, Director, Population Reference Bureau, Washington, D. C.

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## OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF MARCH 6, 1941*

The following case reports and papers were presented:

**Report of Jefferson Hospital Clinics.** Dr. P. F. Williams and A. Behney.

**Two Cases of Abdominal Pregnancy.** Dr. Z. B. Newton.

**The Relation of the Age of the Patient to Prognosis in Carcinoma of the Cervix.** Dr. Pendleton Tompkins.

**Vitamin A in Pregnancy.** Dr. John C. Hirst and Robert E. Shoemaker. (For original article, see page 404, September, 1941, issue.)

*MEETING OF APRIL 5, 1941*

The following paper was presented:

**The Theca Cone, the Pathmaker of the Ascending Graafian Follicle.** Dr. Erwin O. Strassmann, Houston, Texas (by invitation).

*MEETING OF MAY 1, 1941*

The following papers were presented:

**Presidential Address.** Dr. Roy W. Mohler.

**An Available Channel for Improved Obstetrics.** Dr. Owen J. Toland.

**The Etiology and Clinical Significance of Persistent Occipito-Posterior Positions.** Dr. Paul O. Klingensmith.

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Radiation Therapy

Schaefer and Huber: New Method of Roentgen Therapy in Climacteric Bleeding With Conservation of Ovaries, *Strahlentherapie* 64: 557, 1939.

The principles of the new method are the same as in radium treatment, i.e., destruction of the uterine mucosa with utmost protection of the ovaries. Radiation is given with the intraeavitary x-ray tube used in cervical cancer, the anodal part of which can be introduced into the vagina.

Seven patients thus treated and observed for 1½ years after radiation are reported. In most instances bleeding ceased completely soon after treatment; in some cases mild bleeding returned once or twice, to be followed by amenorrhea. One case is mentioned, in which treatment failed to produce amenorrhea and the patient has been menstruating every four to five weeks. This case is instructive for two reasons: (1) It proves that the treatment does not endanger the ovarian function. (2) It establishes the optimal time for irradiation to prevent regeneration of the abraded mucosa. Whereas in all 7 cases radiation was given soon after the curettage, in this case it was given later, probably acting on the mucosa in its hyperplastic glandulocystic state.

As compared with radium, the new method offers the advantage of shorter duration of treatment (one hour by this method, twenty to forty hours with radium) and absence of reactive discharge, which occurs with radium therapy in 66 per cent. With the new method anesthesia is unnecessary, the cervix being sufficiently dilated after curettage for the passage of the aluminum cone.

J. P. GREENHILL.

Morrison, M. C.: Distribution of Radiation in Pervaginal Roentgen Therapy, *Radiology* 34: 451, 1940.

The author describes a method based upon the fact that the chief limiting factor to the administration of a cancericidal dose to any deep-seated tumor is the tolerance of the normal intervening structures, especially the skin. If the deep lesion can be exposed directly to a beam of x-rays without the beam having to traverse normal tissue a cancericidal dose can be safely administered. Carcinoma of the uterine cervix can be exposed through the vagina and treated as a superficial lesion. Daily doses of 450 r. are administered until a total of from 6,000 to 7,000 r. is delivered to the cervix in a period of about two weeks. The usual external roentgen series is given following the local treatment. When supplementary radium treatment is deemed advisable, it is administered as soon as subsidence of the radiation reaction in the vaginal canal permits. The author feels that pervaginal roentgen therapy has a slightly wider distribution of efficient cancericidal radiation than methods of radium application and has the further advantage that over-dosage of the canal region is avoided. In the pervaginal method no area more than 3 cm. from the uterine canal receives more than two threshold erythema doses, so that the bladder and rectum would appear to enjoy

relative protection by this method. He concludes that the daily continuous or interrupted series of pervaginal roentgen treatments would seem to fulfill adequately all requirements in the light of our present knowledge of this factor.

WILLIAM BERMAN.

Bouslog, J. S., and Evans, J. R.: Irradiation of Long Bones for Gynecologic Bleeding, *Am. J. Roentgenol.* 43: 871, 1940.

The writers encountered cases of functional uterine bleeding, intractable to ordinary forms of treatment, in which the only positive abnormal finding was a decreased platelet count. Because there were no other symptoms of purpura, they assumed that the diminution of platelets was due to a deficient formation in the bone marrow rather than to increased destruction by the reticulo-endothelial system (primarily the spleen). Therefore, irradiation of the long bones (100 roentgens to each of the long bones on several occasions) was instituted and the results were immediately successful: the bleeding ceased when the platelet count returned to normal. The disorder has been designated uterine purpura.

J. P. GREENHILL.

Arneson, A. N., and Hauptman, Harry: Radiation in the Treatment of Carcinoma of the Body of the Uterus, *J. A. M. A.* 116: 29, 1941.

This review of the subject indicates the authors' preference for a combined radiologic and surgical therapy. It is felt that hysterectomy alone is inadequate in the treatment of certain types of clinically operable patients, and that average results can be improved by combining radiation with surgery. In the treatment of any one case, certain factors such as the size of the uterus, the presence of infection, and downward extension of the tumor into the cervix should be taken into consideration. It is best to employ preoperative irradiation in all operable cases rather than attempt to individualize the treatment on the basis of the biopsy specimen. The important thing in irradiation is that in every instance an attempt must be made to deliver throughout the tumor-bearing region a dose believed to be adequate for control of the lesion in question. At the same time it is essential that an effort be made to decrease the discrepancy between the minimum dose delivered to some regions and the maximum falling on other points.

The authors feel that by increasing the greater number of irradiating sources, such as by the use of multiple capsules, the minimum tumor dose can be increased without resulting in extensive necrosis of adjacent tissue. They feel that Heyman's technique is one of the most effective methods at our disposal. If one contemplates or feels that infection is present, a preliminary course of x-rays should be used before the insertion of intrauterine radium. The best results are obtained from preoperative irradiation followed by hysterectomy.

WILLIAM BERMAN.

Kotz, J., and Parker, E.: Treatment of Functional Disorders of the Female by Radiation of the Pituitary Gland, *South. M. J.* 33: 832, 1940.

Two hundred and forty-three patients with functional gynecologic derangements, including various menstrual disturbances, sterility, the menopausal syndrome, and miscellaneous conditions, were treated by radiation of the pituitary gland in combination with organotherapy. They were followed for a period of from six months to nine years, averaging two years.

Most ovarian dysfunction is secondary to pituitary failure, the authors state, and therefore it is logical that therapy be directed toward the primary cause. The mode of action of pituitary irradiation is not known, but the end result seems to be that of stimulation. The statement is made that irradiation is not harmful regardless of its effectiveness since regular menstrual cycles were not disturbed by the procedure. Amenorrhea was relieved in 56 per cent of the cases. Irregular periods were relieved or improved in 77 per cent of the patients. While estrogenic hormone therapy usually controls menopausal symptoms, pituitary irradiation

in addition may hasten the response and decrease the duration of treatment. Dysmenorrhea accompanying irregular periods responds well to this combined therapy.

The authors conclude that satisfactory results may be obtained in the treatment of functional menstrual irregularities by a combination of hormone therapy and pituitary irradiation. From their study they are unable to say which of the agents is the more important.

ARNOLD GOLDBERGER.

Rock, Bartlett, Gauld, and Rutherford: The Effect of Subcastrative Roentgen Therapy on Ovarian Physiology, Surg., Gynec. & Obst. 70: 903, 1940.

Twenty-seven cases of menstrual abnormality, with and without associated sterility, are presented. The nature of flow has been evaluated by endometrial biopsy in an effort to determine whether flowing has been of the ovulatory or of the anovulatory type. Subcastrative dosages of x-ray have been employed in an effort to reestablish the normal balance of ovarian function. Endometrial specimens taken before and after x-ray treatment have been used in estimating the value of x-ray treatment to produce ovulation in those patients who do not ovulate or who have only occasional ovulatory cycles. No harmful effects from this treatment upon subsequent pregnancies have been found.

The results indicate that the use of subcastrative doses of roentgen rays is more effective than is the present endocrine treatment. Of the 22 cases of anovulatory flowing, or of infrequent ovulatory cycles, 12 had 3 or more ovulatory cycles following treatment. In 3 of these patients, pregnancy occurred within a short time following treatment.

Contrary to the experience of other investigators, no change after this dosage of x-ray was found in 5 patients with previous normal ovulatory cycles who had the associated complaints of sterility, dysmenorrhea, profuse menstruation, or too frequent menstruation. It is believed that x-ray treatment is indicated only when there is present definite ovarian dysfunction, specifically in those patients who habitually fail to ovulate, as shown by the absence of progestin effect on the endometrium.

Three doses, each of 50 to 60 r., are given over the ovaries of women under 35 years of age. Women older than this may suffer temporary or permanent cessation of follicular function.

It is the authors' opinion that x-ray treatment of the pituitary offers no additional therapeutic benefit.

To explain the good results it is necessary to postulate a destruction by x-ray of persisting mature follicles, thus allowing a new cycle of follicle development and maturation to take place.

WILLIAM C. HENSKE.

Costolow, William E.: Uterine Fibromyomas, J. A. M. A. 116: 464, 1941.

The author reviews and re-emphasizes many well-known and established factors in the treatment of fibromyomas of the uterus. He stresses the importance of careful selection of cases for radiation therapy. Age is an important factor in choosing between radiation and surgery. Fortunately the majority of fibroids are in and close to the menopausal age which makes it somewhat easier for the physician to decide. There is very little evidence in favor of stirring up an acute pelvic cellulitis as a result of irradiating a fibroid in the presence of a chronic pelvic inflammatory condition. This condition, according to the author, could result more easily following a dilatation and curettage and radium application. The author used deep roentgen therapy as well as radium and found the former more applicable in cases of large fibroids, because a large uterus screens out too much of the effect of radium rays on the ovaries.

No case of disability because of radiation menopause could be found in this series of cases, and only 10 patients out of 986 reported any change in "sex desire." Dyspareunia occurred in seven. In tumors the size of a three months' pregnancy or smaller, there was a reduction of the size of the uterus to normal in 84.3 per cent, and to only slightly enlarged in 93.5 per cent of the cases. In uteri

over the size of a 4 months' pregnancy the reduction incidence was reduced to 36.7 per cent. Large pedunculated fibroids show some tendency to degeneration, and should be operated upon if possible. Only 4 of the 986 patients developed carcinoma (3 fundal and 1 cervical), and it is suggested that radiation may have a protective effect in the prevention of malignancy.

WILLIAM BERMAN.

**Chamberlin, Payne, and Stevens: Anuria Following Roentgen Therapy for Pelvic Tumors, Radiology 35: 346, 1940.**

Anuria, due to obstruction of both ureters, is a rare complication during roentgen therapy of tumors within the pelvis. Still rarer is the occurrence of bilateral symmetrical tumors, each involving the lower end of a ureter. The authors have been unable to find any other such case in the literature.

There is a dearth of literature dealing with anuria produced by tissue edema following irradiation therapy. Bugbee has reported 8 and Exley 2 instances of ureteral obstruction following radium therapy for carcinoma of the uterus. All of these, however, may be classified as late effects caused either by continued growth of the tumor, or by fibrosis and constriction due to irradiation therapy. Maintz has cited four instances in which anuria occurred as a complication of roentgen therapy early in the course of treatment for carcinoma of the uterus. His patients remained anuric as long as five days. He attributed the cessation of urinary excretion to swelling of the ureteral mucosa.

There seems to be little doubt that in the case reported by the authors irradiation produced sufficient edema in the tumor to cause a complete bilateral ureteral obstruction. This swelling was evident by rectal and vaginal examinations and also by the fact that the urinary secretion returned several days after roentgen therapy was stopped. In retrospect, it is evident that intravenous urography for the purpose of studying the exact condition of the urinary tract was indicated before roentgen therapy. Furthermore, it must be constantly borne in mind that relatively small doses of irradiation to such tumors may produce local swelling sufficient to obstruct the ureters when the margin of safety has already been reduced.

J. P. GREENHILL.

**Duvergey and Duvergey: Fifteen Cases of Radionecrosis of the Bladder Following Radiation Therapy for Cancer of the Cervix, Compt. rend. Soc. franç. de gynéc. 9: 120, 1939.**

Characteristically, radiation necrosis of the bladder following radium treatment of cancer of the cervix occurs long after the treatment is given. Usually between two and five years elapse, and in one of the authors' cases there was an interval of ten years. Clinically the symptoms are an intense cystitis with pollakiurea, tenesmus, pain, pyuria, and hematuria. In most cases, the impression is given that there is a recurrence of the cancer with invasion of the bladder wall. The way to be certain of the correct diagnosis is to take a biopsy. The usual seat of the bladder necrosis is in the region of the trigone at the base of the bladder at the bladder neck.

Radionecrosis of the bladder is the result of two factors. The first is an intense trophic disturbance caused by the radium and the second is infection. Because of an obliterating endarteritis, there is no vasomotor reaction to combat the infection.

The treatment of this condition consists of disinfection of the bladder by means of daily bladder irrigations with antiseptic solutions. If an ulcer is present it may have to be excised or coagulated. In cases of severe hemorrhage cystotomy may be necessary. Regardless of what is done, it must be remembered that complete cicatrization of the ulcer is a long process so one must have patience.

J. P. GREENHILL.

## Item

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### American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada, on Saturday, January 3, 1942, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination will proceed automatically to the Part II examination held in June, 1942.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Atlantic City, N. J., in June, 1942, immediately prior to the annual meeting of the American Medical Association.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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## Errata

In the article "Tattooing with Mercuric Sulfide for the Treatment of Intractable Pruritus Vulvae and Ani" by Dr. Robert Turell, in the August, 1941, issue of the JOURNAL, page 291, line 7 should read "with Dohi,<sup>6</sup>" instead of "with Aoki.<sup>7</sup>"

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In the article "Lateral Pyocolpos, Double Uterus, Cervix and Vagina, with Absence of Left Kidney" by Dr. Max D. Mayer, in the November, 1941, issue of the JOURNAL, the position of Fig. 7, on page 903, should be reversed as to top and bottom.

9 J. B.	6.4 6.7*	4.0	2.7	1.5	11.5	180 days before	150/100, albumin 4-plus, edema 3-plus
10 M. P.	6.8 5.2 3.4*	3.9 2.3	1.3 1.1	3.0 2.0	11.3	105 days before 42 days before	Delivery of dead child
11 A. B.	6.9 5.3*	4.2	1.7	2.1	13.0	45 days before	190/130, delivery by cesarean, severe toxemia
12 R. Z.	6.7 5.9*	4.2	1.7	2.1	11.1	60 days before	Mild toxemia
13 J. S.	6.7 5.8	4.1	2.6	1.6	12.2	3 days before	Died of eclampsia 4 days later
14 A. D.	7.5 4.9*	4.0	0.9	4.0		180 days before	Eclampsia, 164/110 Albumin 4-plus, Edema 2-plus
15 E. D.	5.9	3.2	2.7	1.2	10.2		Eclampsia? 162/110
16 R. K.	6.0	3.6	2.4	1.5			Pre-eclampsia 205/110
17 M. J.	5.2	3.4	1.8	1.9			Convulsion 170/100
18 M. W.	4.9	3.5	1.4	2.5			168/80, eclampsia
19 D. H.	5.3	3.7	1.3	2.3			Severe eclampsia
20 D. J.	6.0	5.0	1.0	5.0			155/110
21 L. H.	5.0	1.9	3.7	0.6			Hyperemesis earlier
22 H. D.	5.9	4.2	1.7	2.5			Mild toxemia
Average values*	5.4	3.4	1.9	1.8	11.8	Number with inverse ratio 2	Per cent with inverse ratio 9

\*Signifies that the value given was obtained at the height of symptoms, or nearly so.



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proportionate. In a third group, the fall in the ratio value was great although the total protein value was normal or nearly so. The ninth case in the table shows this tendency, while the eleventh belongs to Group 1 and the second to Group 2. In some cases, as for example, the sixth, more than one group is represented among the figures. On the day when the symptoms were at their height, 12 of the patients had high ratios and 8 had low ones.

The previous protein values may have been over 6.0 Gm. until a few days before admission, but a fair number showed a fall in level during the eighth or ninth month, only one case having had low values on all previous examinations.

After delivery, the values rose toward normal. The finding of an average of only 5.4 Gm. for 22 cases at the height of their symptoms may be considered significant. The averages appear at the bottom of Table VII.

One case of hyperemesis gravidarum in early pregnancy followed by late toxemia appears in the table. There were two other cases which could not be put in the table because the patients did not have later toxemia. The first of these had 5.0 Gm. of protein five days before admission. On admission, it was 5.2 Gm. with an a/g ratio of 1.9. Sixteen days later it was 5.0 Gm., at which level it remained until forty-eight days from admission, but the patient did not develop toxemia of late pregnancy. The third woman with hyperemesis had 4.9 Gm. on admission and died of the disease in five days.

Table VIII shows the figures for the hemoglobin determination. There were more women whose hemoglobin was below 10 Gm. toward the end of pregnancy than in the earlier months. The normal and the toxic cases both averaged 11.5 Gm.

In Table IX, the patients with low hemoglobin were grouped according to the color index and cell count. Most of them were hypochromic anemias.

TABLE VIII. OCCURRENCE OF ANEMIA IN THE CLINIC

Months of pregnancy	2	3	4	5	6	7	8	9
Number studied for hemoglobin	21	35	76	92	75	67	43	48
Per cent with 10 Gm. or less	5	5.7	5.2	21.8	20	13.4	7	27.2

TABLE IX. TYPE OF ANEMIA

		AVERAGE HB.	AVERAGE CELL COUNT
All cases studied for type of anemia	23	9.2	3,240,000
Hyperchromic type	5	10.1	2,920,000
Hypochromic type	18	8.9	3,977,000

If 1.5 Gm. of protein per kilo of body weight be taken as the standard for women in the second and third trimesters of pregnancy, only 5 out of the 71 patients whose diets were analyzed ate the standard amount. Their average intake per day was 1.1 Gm./kilo, for both toxic and normal pregnancies. Out of 16 patients who ate only 0.9 Gm. or less, only one had a serum level of more than 6.5 Gm., and this individual later became toxic and the serum level fell.

The individual cases do not show a close correlation between protein intake and serum level. Two possible factors are at work here. Vomiting was severe in several of the women whose serum level was low in spite of a good intake. Utilization of the ingested protein for making serum protein is apparently more complete in women whose intake is low than in those who had a normal diet. This explains why some of the women on low diets did not show very low serum levels. In Whipple's dogs, the number of grams of serum protein manufactured per gram ingested rose as the diet was made progressively poorer. There may be other factors, but in spite of these, a rough relation between the intake and the serum level could be noted.

The intake for the women who later became toxic averaged the same as that of the normals, but the normal women were able to maintain a serum level one-half a gram higher on the same intake.

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In the same group of 16 women who ate less than 0.9 Gm. each day, none had hemoglobin levels over 11 Gm., and most were below 10. The correlation between iron intake and hemoglobin level was poor. The average iron intake was 10 mg. per day for the group.

### CONCLUSIONS

1. A large number of women were studied for anemia and hypoproteinemia in the Philadelphia General Hospital, and the findings are presented.

2. Hypoproteinemia seems to be a reasonably constant finding in both hyperemesis gravidarum and toxemia of late pregnancy. Not many women had toxemia of late pregnancy without some previously existing hypoproteinemia. It has been shown, however, that very prolonged hypoproteinemia was not necessary to the development of toxemia and that some patients on diets sufficient for others to maintain good serum levels go into hypoproteinemia and toxemia. In any attempt to give the etiology of these cases, some factor other than chronic dietary deficiency, some factor which is capable of lowering the serum protein level within a few short days must be sought.

3. The finding of a low serum protein value in a woman in the last trimester of pregnancy is often a warning of impending toxemia, especially if the protein has been normal earlier.

4. The severe anemias were not uncommon in the clinic, but they caused no trouble to any of the patients. Most of them were of the hypochromic type. The relationship between low protein intake and poor hemoglobin formation, earlier reported in dogs, was confirmed in pregnant women. No correlation between serum protein and hemoglobin level nor between the latter and the occurrence of the toxemias was apparent.

I wish to thank Dr. Philip F. Williams and Mrs. Florence G. Fralin for permission to use the data on the diets of these women and for their help and encouragement; also the members of the Department of Chemistry (Postgraduate Hospital) for their advice to me in the chemical determinations.

### REFERENCES

(1) *Strauss, M. B.*: Am. J. M. Sc. 196: 188, 1938. (2) *Ross, R. A., et al.*: AM. J. OBST. & GYNEC. 35: 426, 1938. (3) *Whipple, Geo. H.*: Mellon Lecture 21, 1938, extracted from Am. J. M. Sc. 196: 609, 1938. (4) *Kingsley, Geo. R.*: J. Biochem. 131: 197, 1939.

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# THE EFFECTS OF TESTOSTERONE PROPIONATE, METHYL TESTOSTERONE, ANHYDRO-OXY-PROGESTERONE AND PROGESTERONE UPON LACTATION IN THE NURSING HUMAN BEING

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IN A previous report, it was pointed out that, though afterpains or painful engorgement of the breasts can be adequately relieved by small doses of testosterone propionate (10 to 15 mg.), lactation was not interfered with, provided the baby continued to nurse.<sup>1</sup> Others,<sup>2-4</sup> however, using 40 to 150 mg. of this steroid, have claimed successful inhibition of lactation in the human being. In order to verify our previous observations, the following studies were carried out, using larger dosages of testosterone propionate than any previously reported. In addition, methyl testosterone, anhydro-oxy-progesterone (pregneninolone, ethinyl testosterone), and progesterone were also studied as to their effects upon the initiation of lactation and the maintenance of established milk secretion.

## PROCEDURES AND RESULTS

The mothers and babies used in these studies were carefully selected according to the criteria set up in a previous study.<sup>5</sup> Each gave a history of having adequately nursed a previous child for at least three months. Every one had had a normal spontaneous delivery of a seemingly normal active infant. Starting on the third day, the baby went to breast for twenty minutes at four-hour intervals five times a day. At 2 A.M., a dilute formula was substituted for the breast feeding. By weighing each baby before and after each breast feeding, the daily amount of mother's milk obtained was computed by totaling the results of the five feedings. A minimum of seven and one-half ounces daily was accepted as normal after the third post-partum day.

Fifty mothers served as controls, while there were 36 in the test groups.

*Testosterone Propionate.*—There were 12 patients in this group. To observe the effect of testosterone propionate upon the onset of lactation in the nursing human being, 6 of these received from 200 to 300 mg. of testosterone propionate in sesame oil intramuscularly over a period of two to five days, beginning soon after parturition. In not one instance was the onset of normal adequate lactation delayed (Fig. 1).

To note the effect of testosterone propionate upon established lactation, the other 6 patients received from 250 to 500 mg. of testosterone propionate intramuscularly over a period of two to four days, twenty-four to seventy-two hours after adequate milk secretion had been established. No effect whatsoever was noted upon the amount of milk secretion or upon the baby's gain in weight (Fig. 2).

The effect of testosterone propionate upon painfully engorged breasts has been reported elsewhere.<sup>1</sup>

Clearly, then, provided the baby continues to nurse, testosterone propionate will neither inhibit the normal onset of adequate lactation nor suppress the normal amount of milk secretion after adequate lactation has once been established.

*Methyl Testosterone.*—For the purpose of investigating the effects of this steroid, 10 patients were divided into 2 groups of 5 each. Beginning soon after parturition,



the first group received from 100 to 500 mg. of methyl testosterone in divided oral doses over a period of one to four days. The babies continued to nurse as usual. The onset of adequate lactation was not inhibited (Fig. 1).

In order to observe the effect upon established lactation, the other 5 mothers received from 250 to 500 mg. in divided oral doses twenty-four to seventy-two hours after milk secretion had become adequately established. Lactation was not suppressed (Fig. 2).

*Anhydro-Oxy-Progesterone (Pregneninolone, Ethinyl Testosterone).*—The effect of this steroid upon the initiation of milk secretion was studied in 5 patients. From 100 to 500 mg. were administered orally in divided doses over a period of one to four days, beginning soon after delivery. The onset of lactation was not affected (Fig. 1).

The effect upon established milk secretion was then studied. From 250 to 500 mg. were administered orally over a period of one to four days, starting twenty-four to seventy-two hours after adequate lactation had been established. Milk secretion was not interfered with in any way (Fig. 2).

*Progesterone.*—Because of the difficulty in securing large amounts of this steroid, only 4 patients were studied. Two received 100 mg. in sesame oil intramuscularly over a period of three to four days, respectively, beginning soon after delivery. The onset of adequate milk secretion was not delayed (Fig. 1).

The other two patients received 100 mg. of progesterone intramuscularly in divided doses twenty-four and seventy-two hours, respectively, after lactation had been adequately established. Milk secretion was not suppressed (Fig. 2).

Careful pediatric check-up and follow-up of the babies in the test groups failed to reveal any adverse effects.

#### DISCUSSION

The process of lactation resolves itself into two fundamental mechanisms: the initiation of milk secretion which is under hormonal control<sup>6</sup> and the maintenance of established lactation which is governed by both hormonal and neurogenic factors.<sup>7</sup> These phenomena must be clearly differentiated from the clinical syndrome of painful engorgement of the breasts. The latter is brought about by lymphatic and vascular stasis, not by distention of the ducts by milk.<sup>8</sup> Failure to differentiate clearly the mechanism by which painful engorgement is brought about from the physiological processes leading to the initiation of milk secretion has led to the confusion apparent in the clinical literature. Although painful engorgement may be associated with the onset of lactation, each is a distinct physiologic entity. Clearly then, the one is not synonymous with the other.

In a previous report, it was pointed out that a sufficient daily dose of estrogen (stilbestrol) would delay the onset of adequate milk secretion in the nursing human being only as long as it was administered.<sup>5</sup> The mechanism of action of stilbestrol was felt to be directly upon the glandular epithelium of the mammary gland, for a cell that is actively proliferating (under the influence of estrogen) cannot secrete at the same time.<sup>9</sup> In other words, the ability of a substance to affect the onset of adequate lactation in the nursing mother seemed to parallel its proliferating influence upon the mammary epithelium. The same conclusion was reached by Folley and Kon<sup>10</sup> in their work on rats.

The reason for the failure of the four steroids studied in these experiments (Fig. 1) to affect the onset of adequate milk secretion in the nursing human being becomes apparent from their relatively slight, if any, proliferative effect upon the mammary epithelium.<sup>11</sup> In fact,

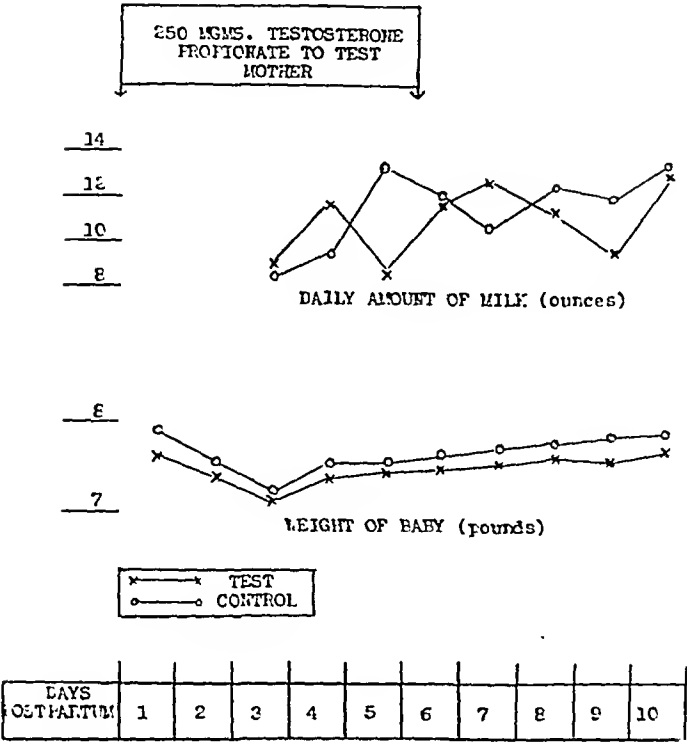


Fig. 1.—Failure of 250 mg. of testosterone propionate to inhibit the onset of adequate lactation in the nursing human being. Similar findings were obtained with either 500 mg. of methyl testosterone or 100 mg. of progesterone, as well as with 500 mg. of pregneninolone.

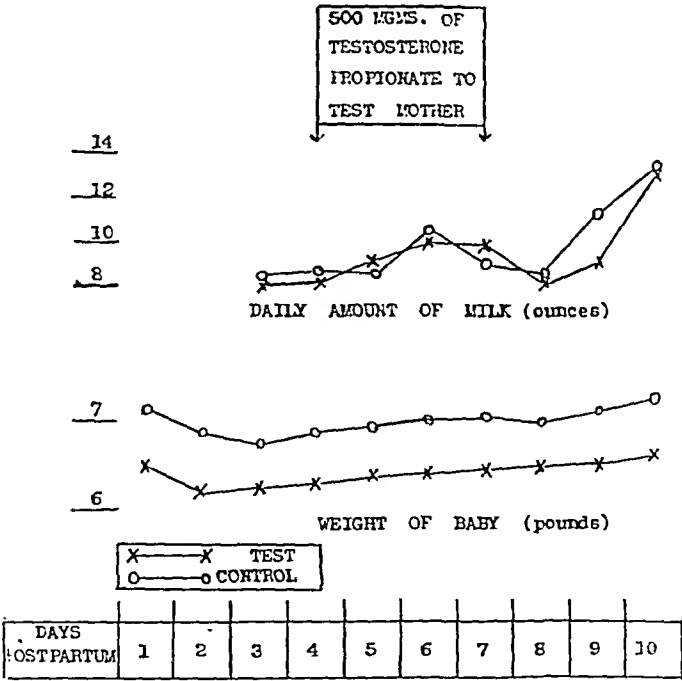


Fig. 2.—Failure of 500 mg. of testosterone propionate to suppress established lactation in the nursing human being. The result illustrated here is similar to that obtained with either 500 mg. of methyl testosterone or 100 mg. of progesterone, as well as with 500 mg. of pregneninolone. Essentially similar results were noted with 500 mg. of oral stilbestrol.<sup>5</sup> Normal variation ranges from one to seven ounces daily.

testosterone, does not depend upon inhibition of lactation but probably involves the shifting tides of extracellular fluid.

The author gratefully acknowledges the sincere interest of Drs. Harry Aranow and Milton J. Goodfriend, during the course of these studies. In addition, the splendid cooperation of the Misses Morgan and Newton, of the Nursing Staff of the Obstetrical Division, is deeply appreciated.

Ciba Pharmaceutical Products, Inc., supplied the following steroids: (1) Testosterone propionate under the trade name of Perandren. (2) Methyl testosterone under the trade name of Metandren. (3) Progesterone under the trade name of Luto-cylin. (4) Anhydro-oxy-progesterone.

#### REFERENCES

- (1) Abarbanel, A. R.: *AM. J. OBST. & GYN.* 38: 243, 1939. (2) Kurzrok, R., and O'Connel, C. P.: *Endocrinology* 23: 476, 1938. (3) Birnberg, C. H., Kurzrok, L., and Klor, S. J.: *AM. J. OBST. & GYN.* 39: 109, 1940. (4) Siegler, S., and Silverstein, L. M.: *Ibid.* 39: 109, 1940. (5) Abarbanel, A. R., and Goodfriend, M. J.: *Ibid.* 40: 1037, 1940. (6) Nelson, W. O.: *Physiol. Rev.* 16: 488, 1936. (7) Selge, H.: *Am. J. Physiol.* 107: 535, 1934. (8) Beck, A. C.: *Obstetrical Practice*, Chap. XVI, Baltimore, 1935, Williams and Wilkins. (9) Reece, R. P., Bartlett, J. W., Hathaway, I. L., and Davis, H. P.: *Proc. Soc. Exper. Biol. & Med.* 43: 186, 1940. (10) Folley, S. J., and Kon, S. K.: *Proc. Roy. Soc., London, Ser. B.* 124: 476, 1938. (11) Astwood, E. B., Geschickter, C. F., and Rausch, E. O.: *Am. J. Anat.* 61: 373, 1937. (12) Reece, R. P., and Mianer, J. P.: *Proc. Soc. Exper. Biol. & Med.* 40: 66, 1939. (13) Reece, R. P., and Turner, C. W.: *Ibid.* 35: 621, 1937. (14) Turner, C. W.: *Sex and Internal Secretions*, Chap. XI, ed. 2, Baltimore, 1939, Williams and Wilkins. (15) Markee, J. E.: *Carnegie Inst. Wash. Pub. No. 518. Contrib. to Embryol.* (No. 177) 28: 219, 1940.

## THE USE OF TESTOSTERONE PROPIONATE IN THE MANAGEMENT OF PELVIC INFLAMMATORY DISEASE

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IT HAS long been recognized that the menstrual period is a time of danger or flare-up in the course of pelvic inflammatory disease. Most patients with chronic pelvic inflammatory disease suffer from dysmenorrhea and/or menorrhagia. Exacerbations of pelvic inflammatory disease at the time of menstruation are so common that often patients are warned to stay in bed before and during their menses to avoid or lessen the chance of a flare-up. Conversely, few patients who manage to retain their infected tubes until the menopause, require surgery thereafter for the relief of the disease, suggesting that cessation of the menstrual function is beneficial in these patients.

The use of testosterone propionate in treating acute and chronic pelvic inflammatory disease was suggested by the ease with which menstruation can be suppressed by relatively safe doses of androgen.<sup>1</sup> It was hoped that not only could the exacerbations be prevented but that inasmuch as there is a natural tendency for large inflammatory masses to regress and even disappear in well-controlled patients, testosterone propionate might prove to be a helpful adjuvant in the management of this disease.

Beclere<sup>2</sup> employed testosterone propionate for uterine hemorrhages with good results. Mazer (C.) and Mazer (M.)<sup>3</sup> used androgen in 38 cases of menstrual disorder, both menorrhagia and metrorrhagia. Greenhill and Freed<sup>4</sup> advocated the use of testosterone propionate in mastopathies, menorrhagia, and dysmenorrhea. Huff-

testosterone greatly stimulates the production by the anterior pituitary of lactogenic principle(s),<sup>12</sup> whose release is actively stimulated by the act of suckling.<sup>13</sup> Consequently, the stimulus of a nursing child was more than sufficient to initiate and then maintain adequate lactation.

Milk secretion, once established, is controlled by both hormonal and neurogenic factors.<sup>7</sup> The manner in which the nervous stimulus of suckling is essential for the continued secretion of milk is still not clear.<sup>14</sup> Upon the clarification of this point must await the explanation for the reason why not only massive doses of these four steroids, but also of stilbestrol,<sup>5</sup> have no effect upon established lactation in the nursing human being (Fig. 2).

The mechanism by which painful engorgement of the breasts is relieved by testosterone propionate and methyl testosterone is not as yet known. That it is not by inhibition of lactation is obvious from the results obtained in these studies (Fig. 1). Its fundamental physiology, however, probably involves the ebb and flow of extracellular fluid in some manner. Markee,<sup>15</sup> for instance, has shown that testosterone will bring about a regression in ocular endometrial transplants as evidenced by a decreased amount of fluid in the stroma and by a lessened vascularity.

#### SUMMARY AND CONCLUSIONS

1. The effects of relatively large doses of testosterone propionate, methyl testosterone, anhydro-oxy-progesterone and progesterone were studied upon the onset of milk secretion and the maintenance of established lactation in the nursing human being.

2. The onset of adequate milk secretion in the nursing human subject was not affected by:

- (a) 200 to 300 mg. of testosterone propionate in oil given intramuscularly
- (b) 100 to 500 mg. of methyl testosterone orally
- (c) 100 to 500 mg. of anhydro-oxy-progesterone orally
- (d) 100 mg. of progesterone given intramuscularly

3. Established lactation was adequately maintained in the nursing woman, being unaffected by:

- (a) 250 to 500 mg. of testosterone propionate given intramuscularly
- (b) 250 to 500 mg. of methyl testosterone orally
- (c) 250 to 500 mg. of anhydro-oxy-progesterone orally
- (d) 100 mg. of progesterone given intramuscularly

4. The ability of a substance to affect the onset of adequate lactation in the nursing woman seems to parallel its proliferating effect upon the glandular epithelium of the breast.

5. Once lactation is adequately established, however, the stimulus for further milk secretion by the glandular epithelium of the breast, produced by an actively suckling baby, proved to be far stronger than the stimulus to proliferation of this same mammary epithelium, provided by massive doses of not only the four steroids used in this study, but also of the estrogen, stilbestrol.

6. The mechanism by which relief of painful engorgement of the breasts is brought about by testosterone propionate, as well as by methyl

during the treatment. After four months, pelvic examination showed persistence of thickening of left adnexa but mass in right side was reduced to 4 cm. She was treated for three months with return of flow at fifth month.

CASE 4.—M. M., white, aged 24 years, single, had subacute pelvic inflammatory disease. Recent gonococcal infection was treated with sulfanilamide, but small masses persisted in both tuboovarian regions, which enlarged at last menstrual period. The period was accompanied by dysmenorrhea. There was complete suppression of flow and relief of expected pain. There had been definite reduction of size of masses when the patient was last seen. Treatment was stopped after two months because of voice changes. She had a period at end of fourth month.

CASE 5.—J. T., white, aged 22 years, married, had a gonococcal infection which was treated with sulfanilamide; then conization of cervix was done. A few months later, she had an acute pelvic peritonitis. There was a 5 cm. mass in the left tuboovarian region. The past few periods had been prolonged, painful, and profuse. She was given testosterone propionate and complete suppression of menses was obtained. There were no flare-ups and the mass was reduced to 3 cm. She was treated three months with return of flow at fifth month.

CASE 6.—R. S., white, aged 39 years, single, had a laparotomy five years previously and a left salpingo-oophorectomy for tuboovarian abscess, but she had refused permission for removal of right tube and ovary which were also chronically inflamed. Dysmenorrhea and menorrhagia persisted, though lessened after operation. She was placed on testosterone propionate with complete suppression of menses and almost complete relief of pelvic pain and diminution in size of pelvic mass. She was treated for three months and injections were stopped because of voice changes and hirsutism. Period occurred at end of fifth month.

An analysis of the above cases shows that menstruation was suppressed in all. No flare-ups occurred during the period of observation. In 5 of the 6 cases, there was definite improvement as judged by diminution of the size of the pelvic masses, and in one case, the pelvic mass completely disappeared. It must be borne in mind that these patients were cooperative and under close supervision, and a certain degree of improvement might have been expected in these circumstances with any or no form of treatment. It is not believed, however, that such uniform results would have been attained without the use of the androgen. We believe that testosterone propionate may also be indicated preoperatively in preparation of patients, who flare up, if only slightly, with each menses, and whom we would like to have as quiescent as possible before operation. Being a reversible reaction and automatically permitting the patient to return to normal function merely by ceasing treatment, testosterone propionate would appear to be far more desirable than x-ray therapy, which may produce irreparable change. Caution must be employed, as virilism, although temporary, may be induced by overdosage.

#### REFERENCES

- (1) Geist, Samuel H., Salmon, Udall J., and Gaines, J. A.: *Endocrinology* 23: 784, 1938.
- (2) Beclere, C.: *Bull. Soc. gynéc. et d'obst.* 27: 747, 1938.
- (3) Mazer, C., and Mazer, M.: *Endocrinology* 24: 599, 1939.
- (4) Greenhill, J. P., and Freed, S. C.: *AM. J. OBST. & GYN.* 39: 636, 1940.
- (5) Huffman, John W.: *Ibid.* 40: 675, 1940.
- (6) Chiray, M., and Mollard, H.: *Presse méd.* 47: 681, 1939.
- (7) Papanicolaou, H. H., Ripley, H. S., and Shorr, E.: *Endocrinology* 24: 339, 1939.
- (8) Rubin, I. C., and Davids, A. M.: *Endocrinology* 26: 523, 1940.
- (9) Geist, Samuel H., Salmon, Udall J., Gaines, J. A., and Walter, R. I.: *J. A. M. A.* 114: 1539, 1940.
- (10) Abarbanel, A. R.: *Endocrinology* 26: 765, 1940.

man<sup>5</sup> suggested the use of androgen therapy in functional uterine bleeding, mastalgias, and puerperal breast engorgement and for the inhibition of lactation and advised further investigation of its use in dysmenorrhea and the treatment of menstrual molimina. Chiray and Mollard<sup>6</sup> used testosterone acetate in the hope of preventing menstrual flare-ups in women with pulmonary tuberculosis in whom menstruation exerts a harmful influence.

According to Papanicolaou, Ripley and Shorr<sup>7</sup> not only is menstruation suppressed by testosterone propionate but there is produced an atrophic endometrium and an atrophic vaginal smear. Rubin and Davids<sup>8</sup> reported that testosterone propionate has an inhibitory effect on the tubal muscle, diminishing its general tonicity and the amplitude of the contractions. Geist, Salmon, Gaines, and Walter<sup>9</sup> summarize the mechanism of testosterone action as (1) inhibition of the gonadotropic factors of the hypophysis, resulting in failure of ovulation and suppression of the normal formation of estrogen and progesterone; (2) direct inactivation of the available estrogens in the body; and (3) the production of androgenic effects (virilism). Abarbanel<sup>10</sup> has recommended the percutaneous administration of testosterone propionate where this is more convenient, although the dosage required is from three to six times as great as that which is necessary by the subcutaneous route.

In attempting to control and treat pelvic inflammatory disease with testosterone propionate, complete suppression rather than mere reduction in amount and duration of the menstrual flow was sought in the patients treated. The average amount of testosterone propionate per month necessary to suppress menstruation varied in these cases between 350 to 650 mg. The drug was administered in 25 to 50 mg. doses, two to three times per week. The subcutaneous method was employed, as it gives better means of control and observation. Due probably to the use of the sulfonamides, fever therapy, Elliott bag therapy, etc., there appear to be fewer cases of chronic pelvic inflammatory disease available for study. The purpose in reporting so small a series is that other workers may attempt this method of treatment, and its value be better assayed.

#### CASE REPORTS

CASE 1.—M. H., white, aged 37 years, married, had had chronic pelvic inflammatory disease for at least two years. There had been frequent flare-ups requiring bed rest. Bimanual examination showed right and left tubal masses 4 and 6 cm., respectively. She was treated for four months with total suppression of menstruation. There were no flare-ups during treatment, and there was less pain and disability reported. Pelvic examination at end of treatment showed reduction in size of masses to 3 cm. each adnexa. Periods had not returned two months after end of treatment.

CASE 2.—E. A., white, aged 33 years, married, had acute pelvic inflammatory disease of gonococcal origin. When first seen, she had pelvic peritonitis with fullness of both tuboovarian regions; exact size of masses was at first undefined. Bed rest and analgesics were prescribed, but no sulfonamides were given and testosterone propionate was instituted. Menses were completely suppressed. There was no exacerbation after the first week. At the end of two months, only tubal thickening was palpable. By the third month, no pelvic pathology was palpable. Cervical and urethral smears were negative repeatedly. This case is not included as an example of desired treatment of acute gonococcal infection, but for illustration of effect of testosterone propionate. We would treat any further cases with sulfonamide plus testosterone propionate. Patient was given treatment for four months, but had not resumed flow two months later.

CASE 3.—S. P., white, aged 36 years, single, had chronic pelvic inflammatory disease many years. She had dysmenorrhea and menorrhagia with every period. Pelvic examination showed thickening of left adnexa and a mass 8 cm. in diameter in right side. Menses were completely suppressed. She received complete relief



## RESULTS

The data in the 500 deliveries routinely instilled are in Table I.

TABLE I. MERCUROCHROME BLADDER INSTILLATION IMMEDIATELY AFTER DELIVERY

TYPE OF DELIVERY	CASES	RETENTION OF URINE LESS THAN 24 HOURS POST PARTUM	RETENTION OF URINE MORE THAN 24 HOURS POST PARTUM	PYELO- URETERITIS
A. Primiparas:				
Normal spontaneous	128	2	0	1
Low forceps	69	1	1	0
Midforceps	19	1	0	0
Assisted breech	13	0	0	0
Breech extraction	1	0	0	0
B. Multiparas:				
Normal spontaneous	240	1	0	0
Low forceps	14	1	1	1
Midforceps	6	0	0	0
Assisted breech	2	0	0	0
Breech extraction	1	0	0	0
Internal podalic version and breech extraction	2	0	0	0
Spontaneous, twins	1	0	0	0
Operative, twins	4	0	0	0
	500	6	2	2

In the instilled series, 8 patients had retention of urine, 2 of these longer than twenty-four hours post partum. Retention of urine was present in only 1.6 per cent of all deliveries. There was no toxic reaction noted from the mercurochrome instillation. Post-partum pyeloureteritis developed in 2 patients; one of these had urinary retention for longer than twenty-four hours, while the other patient

TABLE II. PRIVATE PATIENTS NOT INSTILLED WITH MERCUROCHROME IMMEDIATELY AFTER DELIVERY

TYPE OF DELIVERY	CASES	RETENTION OF URINE LESS THAN 24 HOURS POST PARTUM	RETENTION OF URINE MORE THAN 24 HOURS POST PARTUM	PYELO- URETERITIS
A. Primiparas:				
Normal spontaneous	100	6	1	2
Low forceps	140	23	7	2
Midforceps	55	6	4	1
Assisted breech	10	1	1	0
Breech extraction	2	0	1	0
Forceps to head in breech	4	2	0	0
Operative, twins	1	0	0	0
B. Multiparas:				
Normal spontaneous	138	5	2	0
Low forceps	29	4	1	0
Midforceps	15	3	0	0
Assisted breech	5	2	0	0
Forceps to head in breech	1	0	0	0
	500	52	17	5

had no use of the catheter, except for diagnostic urine culture. Both cases of urinary infection were proved by positive urine culture. The morbidity in the 500 deliveries was 5.8 per cent (100.4° F. used as standard). The one-day fevers

## PREVENTION OF URINARY RETENTION IN THE PUERPERIUM WITH MERCUROCHROME BLADDER INSTILLATIONS

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THE too frequent use of the catheter in a bladder which has become overdistended is acknowledged as a cause for serious urinary tract complications and many methods have been used in an effort to avoid this.

Woodruff and TeLinde<sup>1</sup> reported their experience with prophylactic 0.5% aqueous mercurochrome bladder instillations in a series of gynecologic cases. In their series of 500 laparotomies, there was an incidence of 6.5 per cent of patients with urinary retention, and 0.4 per cent with postoperative pyelitis. In extensive perineal repairs, instillations were reported of little value. Among the recent contributions of significance in connection with physiology and treatment of urinary retention, and pharmacology of the various drugs are the ones by Barber,<sup>2</sup> Moir,<sup>3</sup> Maxwell,<sup>4</sup> Marden and Williamson,<sup>5</sup> Boland,<sup>6</sup> Jordan,<sup>7</sup> Podvinec,<sup>8</sup> and Prather.<sup>9</sup> We have used mercurochrome bladder instillation as a prophylactic measure and in treatment of retention of urine once it has occurred.

At the French Hospital, 2.5 per cent aqueous mercurochrome has been used as bladder instillation immediately following delivery since 1938. The results have been so satisfactory that it has become routine in all clinic deliveries. Any clinic patient not voiding within ten to twelve hours after delivery is catheterized; even sooner if she complains of pain and has a full bladder. We have used intermittent drainage, with catheterization every eight hours for retention. Mercurochrome has been instilled after every third catheterization in these patients. Catheterization for residual urine is used until 50 c.c. or less is obtained.

A study dealing with 500 deliveries followed by routine instillations of 2.5 per cent aqueous mercurochrome is presented. A series of 500 consecutive patients delivered on the private service is reported as control. All patients were delivered in 1940. The study was made on as nearly the normal obstetric patient as possible. For obvious reasons, any patient with ante-partum pyeloureteritis, severe pre-eclampsia, eclampsia, severe cardiac disease, and all premature deliveries (birth weight 5½ pounds or less) is excluded.

### TECHNIQUE

The technique for instilling the bladder is simple. It is done immediately after expression of the placenta and completion of the perineal repair, if one is necessary. The urethral meatus is cleaned with lysol solution, a No. 18 French rubber catheter is inserted, and the bladder emptied. A small funnel is then attached to the catheter, through which 30 c.c. of 2.5 per cent aqueous mercurochrome is introduced by gravity.

c.c. bladder instillation of 2.5 per cent aqueous mercurochrome was given. However, in two of these patients with an overdistended bladder treated in this manner untoward urinary symptoms developed. One patient had hematuria for three days, and the other had pollakiuria which lasted five days. It seems the overdistended bladder mucosa is more sensitive to the mercurochrome and is more likely to toxic reaction.

In the instilled series of cases, it was a fairly common occurrence for the patient to void involuntarily while still under the effect of analgesic drugs. The use of morphine, pentobarbital and scopolamine apparently had no effect on the retention of urine in the instilled series. The type of anesthesia in all the cases, except those delivered with procaine pudendal block and local perineal infiltration, was nitrous oxide-oxygen mixture, supplemented by ether in a closed system. No attempt was made to evaluate the effect of anesthesia on urinary retention. There were no bladder injuries in either series of cases. Dührssen's incision in the cervix was not done. However, 3 cases required suturing of a cervical laceration after delivery. The repairing of an episiotomy or perineal laceration apparently had no relation to retention of urine. All patients had pelvis ample for full-term deliveries per vaginam.

#### SUMMARY AND CONCLUSIONS

1. Aqueous solution of mercurochrome for bladder instillations as the prophylactic preventive and treatment of retention of urine in the puerperium is outlined.

2. Of the cases in the instilled series, 1.6 per cent and, of the cases in the control series, 13.8 per cent had puerperal retention of urine. This is approximately a 9 to 1 difference.

3. Post-partum pyeloureteritis was a complication in 0.4 per cent of the routinely instilled patients, and 1.0 per cent of the control series.

4. Frequent bladder catheterization in the presence of retention of urine was an important cause of post-partum pyeloureteritis.

5. Primiparas in whom operative deliveries were done were the most frequent patients to develop retention of urine.

6. The repair of an episiotomy or perineal laceration had no relation to retention of urine in the puerperium.

7. The incidence of urinary retention was related to the duration of the labor.

8. No correlation was found between retention of urine and the use of analgesic drugs.

9. No toxic effects were noted from the mercurochrome in the instilled series of patients.

10. Sensitivity to the mercurochrome was observed in the overdistended bladder. Mercurochrome should be used with caution in these patients.

#### REFERENCES

- (1) Woodruff, J. Donald, and TeLinde, Richard W.: J. A. M. A. 113: 1451, 1939.
- (2) Barber, H. S.: Irish J. M. Sc. 6: 68, 1938. (3) Moir, Chassar: Lancet 1: 261, 1937. (4) Maxwell, J. S.: Lancet 1: 263, 1937. (5) Marden, Philip A., and Williamson, Ernest G.: Surg., Gynec. & Obst. 69: 61, 1939. (6) Boland, Frank K., Jr.: Urol. & Cutan. Rev. 43: 323, 1939. (7) Jordan, Claus G.: Ann. Surg. 98: 125, 1933. (8) Podvinec, J.: Bull. Soc. d'obst. et de gynéc. 25: 503, 1936. (9) Prather, G. C.: AM. J. OBST. & GYNEC. 17: 215, 1929. (10) Randall, Lawrence M., and Murray, Stephen E.: J. A. M. A. 101: 2023, 1933.

were 4.2 per cent. There were 5 prolonged labors (thirty hours or more), and 36 short labors (three hours or less). The total operative incidence was 26.2 per cent. Three third-degree lacerations were repaired.

### RESULTS

The data on the private patients who had no bladder instillation immediately following the delivery are tabulated in Table II.

There were 52 patients among the private patients with retention of urine, who required catheterization one or more times in the first 24 hours post partum. Seventeen patients had serious retention of urine for longer than twenty-four hours. The total percentage of patients having urinary retention was 13.8 per

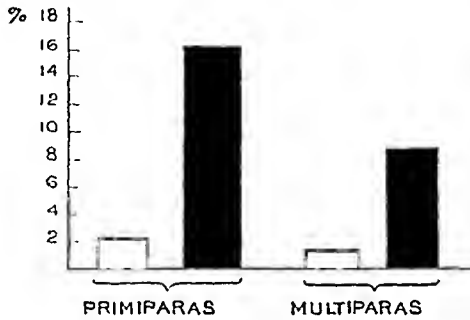


Fig. 1.—Percentage of patients with retention of urine.

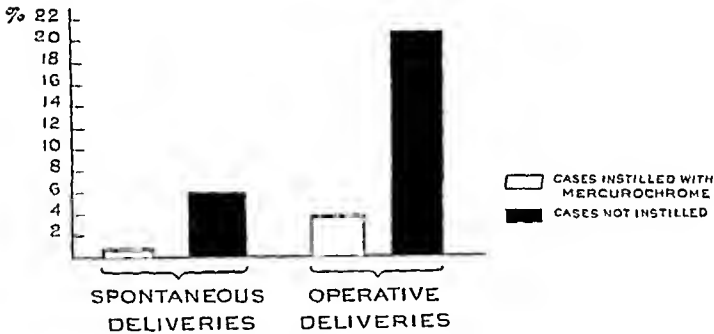


Fig. 2.—Percentage of patients with retention of urine.

cent.' Randall and Murray<sup>10</sup> report 15 per cent of puerperal women require catheterization. It is noteworthy that 5 patients developed post-partum pyeloureteritis, 4 of these having urinary retention before signs and symptoms of urinary tract infection became evident. One of the patients catheterized for longer than twenty-four hours developed pollakiuria. The morbidity was 3.4 per cent in this series while the one-day fevers were 6.4 per cent. The operative incidence totaled 52.4 per cent. There were 14 short labors and 11 prolonged labors. One third-degree laceration was repaired.

Fig. 1 shows the percentage of cases in both series of 500 deliveries divided according to parity. The spontaneous and operative deliveries in which the catheter was used for retention of urine in the puerperium is illustrated in Fig. 2. It is well shown in the charts that primiparity associated with operative delivery was by far the most frequent case to develop post-partum retention of urine. In more than half of the primiparas with retention of urine, the duration of labor was more than twenty hours. Randall and Murray<sup>10</sup> emphasize the highest percentage of puerperal urinary retention in the longer labors.

Orders for post-partum catheterization in the private cases varied from eight to eighteen hours. After retention of urine had developed in 14 private cases, a 30



Fig. 1.—Case 1. Appearance of prolapse on admission showing ulceration, edema, and hypertrophy.



Fig. 2.



Fig. 3.

Fig. 2.—Case 1. In labor, station of head just before Dührssen's incisions were made. A, Fetal scalp; B, anterior lip of cervix.

Fig. 3.—Case 1. Appearance of the cervix at time of discharge. A, B, C, healed Dührssen's incisions.

## PROLAPSE OF THE UTERUS DURING PREGNANCY

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PREGNANCY associated with marked prolapse of the uterus is rare; only one such case has been observed among more than thirteen thousand obstetric admissions at the University Hospital between January, 1926, and July, 1940. At the Wisconsin General Hospital\* there was a similar case among two thousand admissions between Jan. 1, 1930, and Jan. 1, 1940, the patient having had four pregnancies since the onset of the procidentia. The third case† was reported by a private practitioner in Wisconsin.

CASE 1.—V. M. (Hosp. No. 40-1081), a 28-year-old, married, white secundigravida, was admitted to the University Hospital, Iowa City, Jan. 24, 1940. The last menstrual period began May 16, 1939, making the expected date of delivery Feb. 23, 1940.

The patient had developed a band type of scleroderma with muscular atrophy at the age of eight years. The skin changes were distributed irregularly over the face, trunk, and extremities. The first pregnancy had ended in a normal, spontaneous delivery in 1934. Several months later a persistent incomplete prolapse of the uterus was noted.

During the first months of this second pregnancy, there were no complaints, but six weeks prior to admission the cervix rapidly became larger and longer, and there was daily "spotting." Later the organ attained such a size and protruded so far beyond the introitus that walking was difficult.

On admission the cervix, which was hypertrophied and elongated, protruded 10 cm. beyond the introitus; it was cone-shaped with the largest diameter about the external os, at which level the circumference was 22 cm., while at the introitus it was 15 cm.; there was marked erosion and ulceration about the external os from which hung a small mucous polyp. The uterus extended to within 6 cm. of the xiphoid; the fetus was in R.O.A. position, and the fetal heart was audible in the right lower quadrant; there was no evidence of pelvic disproportion.

*Course in the Hospital.*—Bed rest in slight Trendelenberg position with a heat cradle over the body was prescribed. Warm glycerin packs, containing 5 per cent mercurochrome, were applied to the cervix for one-half hour three times daily. As the size of the cervix diminished, it was pushed gently into the vagina, which was packed lightly. However, it was never possible to prevent recurrence of the prolapse for more than twenty-four hours. The erosion healed gradually. Despite the fact that the fetal head was engaged and the baby seemed of mature size, the patient had not gone into labor by March 1. On that day and again on March 6 unsuccessful attempts were made to induce labor medically. On March 11, 500,000 international units of progynon B in oil were given intramuscularly. Twenty-four hours later labor began spontaneous.

After ten hours in the first stage of labor, which had progressed normally, the head was on the pelvic floor and the scalp was visible. The cervix was dilated 4 to 5 cm. and well effaced. At this point labor stopped and for the next twelve hours there was no progress. It was then decided to effect delivery by cervical incisions and forceps. The baby was a normal male weighing 3,255 Gm.

\*This case report was made available through the courtesy of Dr. J. W. Harris, University of Wisconsin Medical School, Madison, Wisconsin.

†This case report was made available through the courtesy of Dr. F. A. Wendt, Johnson Creek, Wisconsin.

TABLE I. SUMMARY OF 170 CASES OF UTERINE PROLAPSE DURING PREGNANCY

SOURCE	YEAR	TOTAL NO. OF CASES	CASES WITH DATA	OPERATION DURING PREGNANCY	ABORTIONS	SPONTANEOUS DELIVERIES	FORCEPS	VERSIONS	DÜHRSEN'S INCISIONS	CRANIOTOMIES	CESAREAN SECTION	FETAL DEATHS	MATERNAL DEATHS
1. Franke	1892	124	116	6 plastic repairs	20	51	29	6	34	10		26	5
2. Seitz, Ludwig	1901	9	Included in above										
3. Andrews, H. C.	1906	4	4	1 plastic repair		3	1		1			1	1
4. Findley, Palmer	1911	10	3		1 therapeutic abortion (with plastic repair)		2		2			1	
5. Hertzler, A. E.	1911	1	1			1							
6. Dorsett, W. B.	1911	1	1			1							
7. Harris, J. C.	1912	1	1		1 therapeutic abortion								
8. Solomons, B.	1912	2	2	1 plastic repair	1	1							
9. Barton	1912	1	1 (Partial data)									1	1
10. Kennedy	1912	1	1 (Partial data)									1	1
11. Maurizia, B.	1912	1	1			1							
12. Faivre	1918	1	1				1						
13. Maxwell, J. C.	1925	4	4				3		3	1		1	1
14. Williams, J. W.	1930	1	1										
15. DeLee, J. B.	1933	3	3										
16. Higgins, D. E.	1934	1	1										
17. Serbin, W. B.	1934	2	2			2			1				
18. Keetel, W. C.	1940	3	3			4*	2						
Totals		170	142 (140 complete data)	8	23	64	38	6	41	11	1	31	9

\*One patient delivered 4 times.

The puerperium was afebrile and uncomplicated except for a right Bell's palsy which developed on the third day after delivery. At the time of discharge on the thirteenth day the cervix protruded 1 cm. beyond the introitus, and the incisions were well healed.

*Follow-up.*—The patient returned to the Hospital June 4, 1940. There was no complaint except the prolapse. The cervix protruded 2 to 3 cm. beyond the introitus and could be pulled out that much farther. The Dührssen's incisions were scarcely visible. The uterus was retroverted and enlarged slightly. Both adnexa were free. The facial palsy had disappeared completely. Vaginal hysterectomy and plastic repair were done on June 7. Pathologic examination showed hyperplasia of the endometrium and uterine endometriosis. The postoperative course was satisfactory and the patient was discharged June 17.

CASE 2.—J. R. (Hosp. No. 35280), a 26-year-old, married, white, octipara, was first admitted to the Wisconsin General Hospital in 1928. At that time she indicated she had had a normal delivery in 1925 and twins in 1927 with no complications. In 1928, her first admission to Wisconsin General Hospital, a hydrocephalic monster was delivered after craniotomy. No mention was made at this time of any relaxation of the vaginal outlet. The fourth gestation, in 1929, was associated with a marginal placenta previa; a living child was obtained by version and extraction. Incomplete procidentia appeared in the second week of this puerperium.

During the next seven years the patient had four more deliveries, January, 1932, May, 1934, June, 1935, and April, 1937. With each of these later pregnancies, there was marked uterine prolapse, and signs of threatened abortion appeared during the gestation period in 1932.

The cervix which often protruded beyond the introitus was hypertrophied, eroded, and badly lacerated. At each delivery, the fetal head could be seen through the dilating cervix. The labors were normal and the deliveries were spontaneous. The uterus was packed after one delivery to control bleeding, and at the time of the last confinement there was a severe post-partum hemorrhage due to uterine inertia, and the fact that it was not possible to massage the fundus. All puerperiums were afebrile. The babies were normal, weighing more than 2,500 Gm. each at birth. After each of the last four deliveries, surgical repair and sterilization were recommended, but were refused because of religious convictions.

CASE 3.—K. W., a 43-year-old, married, white, secundipara, was first seen Dec. 1, 1939. The two previous deliveries had been uncomplicated. The prolapse was first noticed in 1937 and had gradually increased. The patient was in good physical condition, the only positive findings were a four and one-half months' pregnancy associated with marked prolapse. The cervix which protruded 6 cm. beyond the introitus was edematous and partially ulcerated. During the next few weeks the patient's activity was limited. After the seventh month complete bed rest was ordered. During the period of rest the ulceration and edema almost entirely disappeared under local applications of silver nitrate.

The patient was hospitalized immediately at the onset of labor. Dr. Wendt's comment on the course of labor was "Watchful waiting was the main item in this delivery and I never felt it necessary to be radical and do a section. It was interesting to watch the progress as the cervix was completely outside the introitus and one could watch the dilation which was slower than usual, until pressure was applied to the cervix to hold it back in the canal." The child then was delivered by low forceps. The baby was normal and the puerperium was uneventful. Several months later a total hysterectomy and plastic repair were performed.

#### LITERATURE

Based upon the number of cases reported, it is apparent that prolapse of the uterus associated with pregnancy is unusual. Most of the recorded cases that have gone to term showed only an elongated, hypertrophied and edematous cervix. The first and third cases above are of this type. Complete procidentia is hardly compatible with a full-term gestation.



Seitz<sup>14</sup> he was of the opinion that repair should be done without interruption of the pregnancy.

Patients who did not abort frequently improved after the fourth or fifth month of pregnancy, because the uterus rose out of the pelvis pulling the cervix into the vagina. Among the earlier cases Franke,<sup>7</sup> Seitz,<sup>14</sup> and Maurizia<sup>12</sup> all recommended a pessary to hold the cervix in the vagina during the early months of gestation with removal of the appliance as the uterus enlarged and the cervix was drawn upward. Seitz<sup>14</sup> even advised anesthetization of the patient and replacement of the uterus with insertion of a pessary regardless of the duration of the pregnancy.

It was felt by Andrews<sup>1</sup> that the incidence of breech presentation was increased, but he offered no statistical evidence to support his opinion.

The operative incidence was extremely high in the reported cases. The most common method of delivery, excluding spontaneous expulsion, and perhaps the safest operative procedure were the use of forceps after Dührssen's incisions, which are easily made with the cervix presenting. Exposure is excellent and the cervix is usually well effaced. Version and extraction, craniotomy, and cesarean section were used only occasionally.

The fetal death rate was high. This was largely explained by the need for operative intervention, the prolonged labors, and the number of premature infants.

Among the 14 cases of maternal sepsis there were 8 deaths (57.1 per cent). The number of severe infections was not great considering the operative incidence, the prolongation of labor, and the fact that delivery was made through a potentially infected field. Before 1911, when puerperal infections were more common, there were 6 deaths in 120 cases, a mortality rate of 5 per cent; yet from 1911 to 1940 there were 3 deaths in 22 cases, a death rate of 13.6 per cent.

#### SUMMARY

Three women having prolapse of the uterus associated with pregnancy are presented. One hundred and sixty-seven other reports have been collected from the literature. The outstanding features associated with this complication are the frequency of abortion, the high operative incidence to effect delivery, and the high percentage of fetal and maternal deaths. The treatment was formerly radical, but in recent years has been conservative. Aside from spontaneous expulsion, which is frequently possible, the simplest and safest method of delivery is low forceps following Dührssen's incisions.

#### REFERENCES

- (1) Andrews, H. C.: Clin. J. 28: 221, 1906.
- (2) Barton, quoted by Solomons, B.: J. Obst. & Gynaec. Brit. Emp. 21: 155, 1912.
- (3) DeLee, J. B.: Principles and Practices of Obstetrics, Philadelphia, 1936, W. B. Saunders Co.
- (4) Dorsett, W. B.: J. A. M. A. 57: 2133, 1911.
- (5) Faivre quoted by Hirst, B. C.: Text-Book of Obstetrics, Philadelphia, 1918, W. B. Saunders Co.
- (6) Findley, P.: J. A. M. A. 57: 2131, 1911.
- (7) Franke quoted by Seitz, L.: Ber. ü. d. ges. Gynäk. u. Geburtsh. 6: 244, 1901.
- (8) Harris, J. C.: J. South Carolina M. A. 8: 248, 1912.
- (9) Hertzler, A. E.: J. A. M. A. 57: 2133, 1911.
- (10) Higgins, D. E.: New England J. Med. 211: 125, 1934.
- (11) Kennedy quoted by Solomons, B.: J. Obst. & Gynaec. Brit. Emp. 21: 155, 1912.
- (12) Maurizia, B.: Arte Ostet., Milano 26: 105, 1912.
- (13) Maxwell, J. C.: China M. J. 39: 479, 1925.
- (14) Seitz, L.: Ber. ü. d. ges. Gynäk. u. Geburtsh. 6: 244, 1901.
- (15) Serbin, W. B.: AM. J. OBST. & GYNEC. 27: 910, 1934.
- (16) Solomons, B.: J. Obst. & Gynaec. Brit. Emp. 21: 155, 1912.
- (17) Williams, J. W.: Obstetrics, New York, 1930, D. Appleton-Century Co.

However, cases have been observed that went to the seventh lunar month with the uterus outside the body before delivery occurred.

The *Index Medicus* revealed 170 reported cases of pregnancy associated with more or less complete uterine prolapse, 137 of which were collected before 1901 by Franke,<sup>7</sup> Seitz,<sup>14</sup> and Andrews.<sup>1</sup> Palmer Findley,<sup>6</sup> in 1911, made the last review and added 10 cases. Twenty-three other reports have appeared in the interval, including the 3 here reported. Clinical data were available in 142 of the 170 cases, with complete data on 140.

*Parity.*—Among the 170 recorded cases, there were 19 primigravidas, 82 multigravidas, and 69 individuals on whom no data were available. Trauma was cited as the most frequent cause of prolapse among the primigravidas.

*Complications of Pregnancy.*—The majority of these women had been aware of the prolapse before conception. Many authorities offered the comment that fertility was not altered. The second individual recorded here illustrates this point, since she had become pregnant four times following the onset of the procidentia. In several instances prolapse developed after the onset of the pregnancy, and Maxwell<sup>13</sup> feels that such an occurrence can be attributed to sudden trauma or straining. Many patients were reported as uncomfortable and even bedridden because of the protruding mass.

Among the 140 cases with adequate clinical data, there were 21 spontaneous abortions, or 15 per cent. There is no definite explanation for this high incidence of abortion, except that it may be due to temperature changes and trauma. There were only two therapeutic abortions, or 1.4 per cent; one was accomplished by vaginal hysterotomy, combined with anterior and posterior wall repair and cervical amputation; the other was terminated by total hysterectomy at the fifth month.

Eight, or 5.7 per cent, had either anterior and posterior wall repairs or cervical amputations between the second and fifth months of pregnancy. None of these patients aborted and all were delivered spontaneously.

*Delivery.*—Delivery was normal in 64, or 45.7 per cent, of the cases; 38, or 27.1 per cent, were delivered by forceps, mostly low applications following Dührssen's incisions. Eight fetal deaths occurred in this group. Dührssen's incisions were employed 41 times, or in 29.3 per cent of the total. The infants were usually extracted by forceps, but on several occasions spontaneous delivery occurred. Faivre<sup>5</sup> reported one case where the assistant pushed the cervix back over the baby's head so that the delivery occurred normally; Case 3 also demonstrated this procedure.

Delivery was effected six times, 4.3 per cent, by version and extraction with two fetal deaths. Craniotomy was done 11 times, 7.8 per cent, including 3 operations involving living fetuses. Ten of the craniotomies were reported by Franke<sup>7</sup> and Seitz.<sup>14</sup> Cesarean section was performed once; the operation was of the Porro type with fixation of the cervical stump. Harris<sup>8</sup> advocated that every woman with prolapse should have this type of treatment.

*Fetal Deaths.*—Thirty-one babies died during, or immediately after, delivery, making a fetal death rate of 22.1 per cent. While it was impossible to compile accurate data, it was noted that premature delivery was frequent.

*Maternal Morbidity and Mortality.*—Morbidity data were available on only 112 and mortality data on 142 women. Fourteen were grossly infected, an incidence of 12.5 per cent. There were 9 maternal deaths, or 6.3 per cent. One death was due to perforation of the uterus and eight to infection.

#### COMMENT

Prolapse of the uterus is rightly considered a serious complication of pregnancy. The condition apparently has little effect upon fertility, and pregnancy frequently occurs in spite of marked chronic cervicitis. Early abortion is relatively frequent. Therapeutic abortion has been seriously advocated, and Findley,<sup>6</sup> in 1911, recommended interruption of the pregnancy followed by plastic repair, provided the patient were incapacitated during the early part of pregnancy and showed no improvement following bed rest. Later upon learning of the work of

The Baldy-Webster operation, by suturing the round ligaments brought through the broad ligaments to the posterior uterine wall, distorts the normal relationship of the round ligaments to the uterus and broad ligaments and, at the same time employs the weaker portion of the round ligaments for support. This operation is not suited for a heavy uterus.

The Olshausen operation makes use of the stronger portion of the round ligaments and raises the pivotal point of the uterus; but by suturing these ligaments to the parietal peritoneum and causing the uterus to suspend indirectly therefrom, it, likewise, distorts the normal relationships of these ligaments, the uterus, and involved peritoneum.

The Bissell operation, by the intraligamentous shortening of the broad ligaments, also raises the pivotal point of the uterus, an ideal procedure for slight uterine descent. It depends upon section and duplication of the round ligaments for maintenance of the corrected retroversion. This operation is technically difficult, time-consuming, and has a recurrence of 4 per cent.

The fact of the prevalence of so many methods for the treatment of retroversion is evidence that none of these operations has met adequately the major requirements for ultimate satisfactory results, generally.

Hence, a method anatomically sound, physiologically planned, free of the shortcomings of former methods and having a percentage recurrence less than that of former methods seemed timely and desirable. Such is the nature of the method developed and about to be described based on the treatment of 300 cases of uterine retroversion in our service during the past fifteen years with a recurrence of only 2 per cent. It is with the view that the successful employment of this operation, by others, for the correction of the types of nonpuerperal retroversion, designated above, may warrant widespread acceptance that this report is presented.

#### THE UTEROLIGAMENOTOPEXY OPERATION

Due credit must be given to Dougall Bissell, the first to trace, by dissection, the thin layer of subperitoneal abdominal fascia into the uterine ligaments.

Initiation of this operation was based on the recognition of that fact; and its possible development was predicated on knowledge that the utilization of fascia would be as fundamentally essential to ultimate support and satisfaction, here, as it is for a successful hernial operation or other gynoplastic technology.

#### TECHNIQUE

The usual midline or paramedian incision is made sufficiently long to admit freely one hand into the abdominal cavity. The uterus, tubes and ovaries are sought and freed of any complicating adhesions and/or fibroids. The fundus of the uterus is then brought forward manually to a point that parallels its body with the direction of the pubic symphysis. Care is taken not to anteflex the uterus, for, by so doing, the line of force of intra-abdominal pressure in the erect position would be directed against the posterior wall of the uterine body, producing eventually pathologic anteflexion, a condition less desirable. By placing the uterus as stated above in the erect position, the abdominal pressure is directed against the posterior half of the uterine fundus, forcing the latter slightly forward (anteflexion) against the pubic arch which absorbs this force and prevents uterine descent.

## UTEROLIGAMENTOPEXY OPERATION FOR RETROVERSION OF THE UTERUS (NONPUERPERAL)

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THE development of a surgical method for the satisfactory correction of retroversion of the uterus, especially during the childbearing period, has been a perennial challenge to the ingenuity of gynecologists. As a consequence various methods have been devised, from time to time, and their results have been not infrequently disappointing, having, among other shortcomings, 4 to 15 per cent recurrences.

Forty-one per cent of uterine retroversions are represented by the puerperal type which, although most symptomatic, is likewise the most remediable through the early use of nonsurgical measures, such as the knee-chest position, monkey walk, or the Smith-Hodge pessary.

On the other hand, asymptomatic retroversion allowed to continue uncorrected is destined to prejudice the well-being of women who menstruate by (1) pressure symptoms, (2) uterine adhesions conducive of abortion, (3) twisting of the tubes and the pointing of the portio vaginalis favoring infertility, (4) chronic passive congestion of the uterus followed by myometrial replacement with fibrous tissue, producing a menorrhagia progressive and from which effective relief is obtainable only by hysterectomy, bilateral oophorectomy, or x-ray menostasis with inevitable and unpredictable consequences. The early correction of this type of retroversion would inaugurate a prophylactic policy productive of gratifying returns in the preservation and promotion of functions involved.

It is the symptomatic type with no menorrhagia, however, with which we are chiefly concerned.

It might not be amiss, here, to make a critical review with comments on a few of the prevalent methods employed.

The Alexander operation, in addition to being a rather blind procedure and depending for support solely on use of the weaker portion of the round ligaments, is totally unsuited in cases with complicating adhesions or large fibroids. This operation has a recurrence of 15 per cent. The "internal Alexander operation" is an improvement.

While in the Gilliam operation the stronger portion of the round ligaments is attached to the fascia of the abdominal wall, it is attached indirectly also to the sensitive parietal peritoneum and at the same time creates an opening through which a loop of gut could become incarcerated and even strangulated. Simpson's modification of this operation offers some improvement.

The Ferguson operation, also, causes an indirect attachment of the round ligaments to the parietal peritoneum and, besides, renders these ligaments extra-abdominal structures.

The Coffey operation, an imbrication of the upper and stronger portion of the round ligaments across the anterior uterine wall, utilizes likewise only the round ligaments, fibromuscular structures, for support.

fascia at a distance sufficient from the uterus and ends with a similar bite through the corresponding point on the uterus lateral to the origin of the respective round ligament. Similarly, each catgut suture starts on the broad ligament with a bite including the depth of the round ligament and, after two or three such bites, ends with a deep bite at the point on the uterus between and slightly above the attachments of the silk sutures.

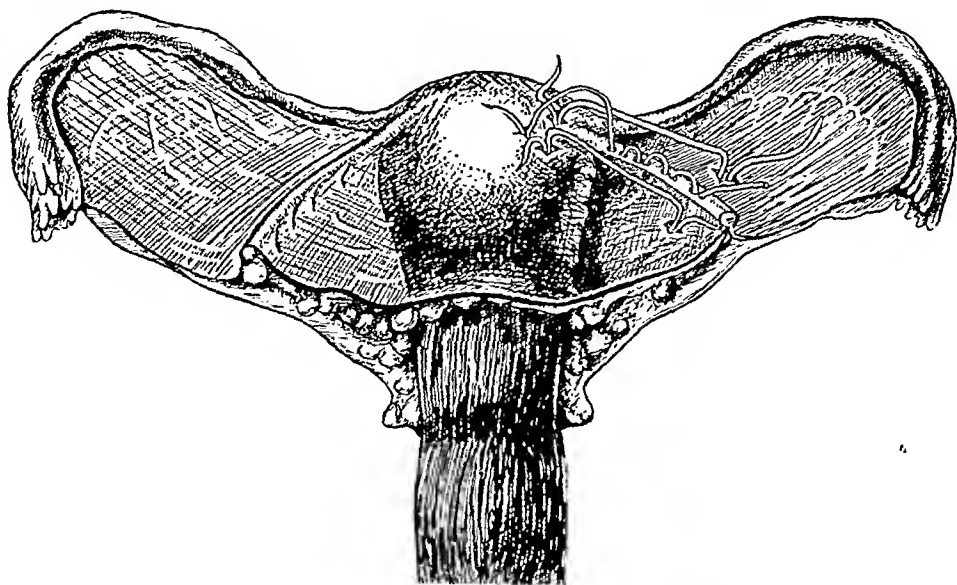


Fig. 3.—Showing placement of sutures in broad and round ligaments.

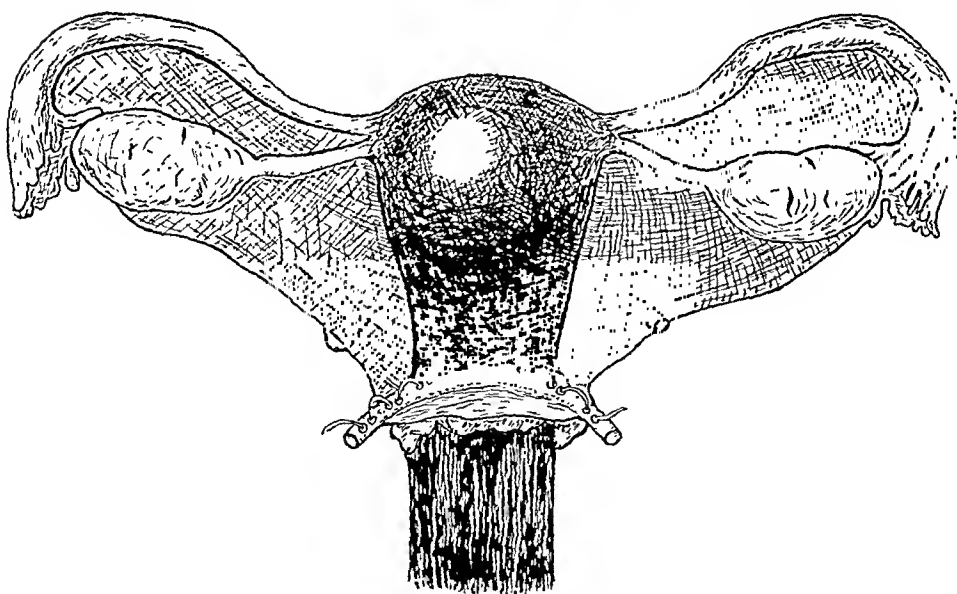


Fig. 4.—Showing sutures in uterosacral ligaments.

The corrected uterus is thus fortified with six new points of fascial attachments rendering the operation anatomically constructed and physiologically designed to insure ultimate therapeutic effectiveness.

Changing the fundus from the retroverted position shifts, concomitantly, the pointing of the portio slightly dorsad, producing corresponding slack in the uterosacral ligaments. This slack is taken up with a deep gathering stitch of heavy

With the fundus so placed, slack is created in the round ligaments and the anterior fold of each broad ligament. Maintenance of the fundus in this corrected position and taking-up this slack are effected by the attachments of three calculated points, roughened or denuded of serosa on the anterior fold of each broad

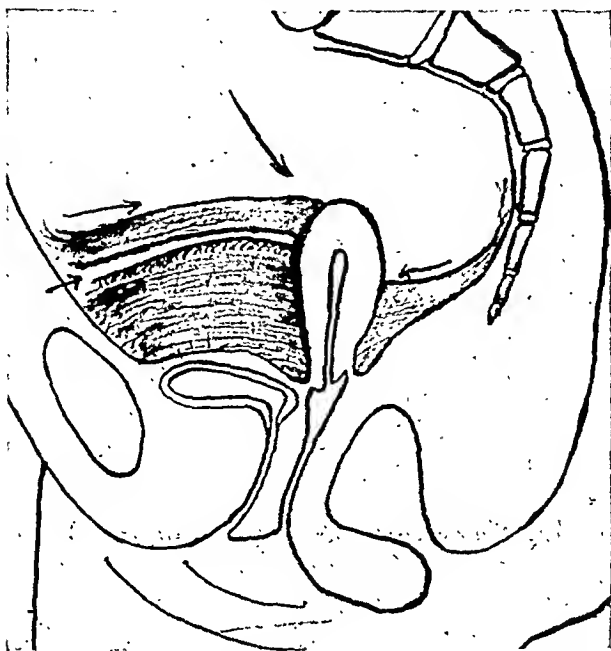


Fig. 1.—Retroverted uterus showing broad, round, and uterosacral ligaments stretched and showing direction of intra-abdominal pressure against anterior surface of fundus uteri.

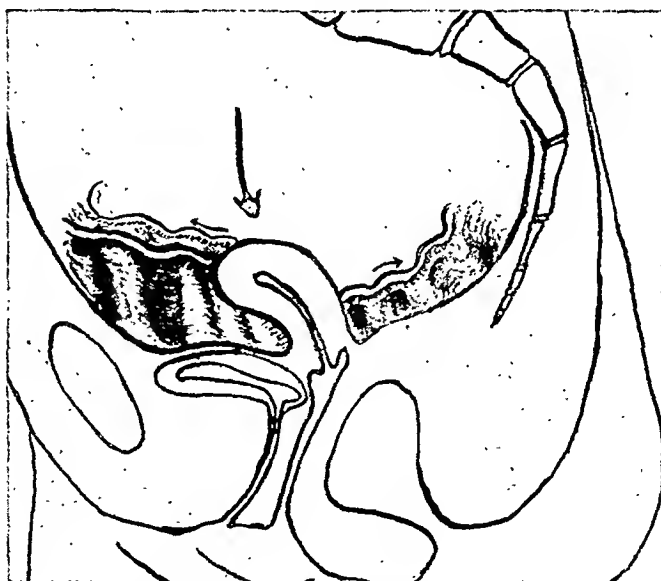


Fig. 2.—Uterus corrected, showing slack in ligaments and direction of intra-abdominal pressure against posterior surface of fundus uteri.

ligament, to corresponding roughened points on the anterior surface of the uterus by use of four No. 5 braided silk and two No. 2 chromic catgut sutures, as follows: Each silk suture in a round needle is started at a point on either side of the round ligaments with a generous bite of broad ligament tissue, including the subjacent

# HUMAN THORACOPAGUS MONSTER (SO-CALLED SIAMESE TWINS)

## CASE REPORT AND ANATOMICAL STUDY

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**H**UMAN fetal monsters are rare, and it is, therefore, an exceptional opportunity to be able to examine a full-term double monster in detail. Interest in double monsters has been recently stimulated by the re-publication of the autopsy report of the original Siamese twins.<sup>1</sup> The case we are reporting is of especial interest, because it is only the second of its kind in a total of 82,000 deliveries at the Cook County Hospital since 1905. Ysander<sup>2</sup> in his monograph states that there were 226 known cases of thoracopagus tetrabrachius tetrapus reported in the literature up to 1911. His search through 1922 added 42 more cases, bringing the total to 268. We have found 63 additional cases, including our own, reported since that time to date, increasing the total to 331.

Mrs. E. K., white, aged, 39 years, gravida iii, para ii, entered Cook County Hospital at 5:50 P.M. on July 29, 1940, in labor, having moderate pains every four minutes. She had had two previous normal full-term pregnancies, delivered at home. There was a history of twins on both sides of her family.

Physical examination showed the patient to be in good condition. Her blood pressure was 116/80, and the urine was negative for albumin. The blood Wassermann test was negative, and the smears negative for gonococci.

Rectal examination revealed the cervix about 5 cm. dilated with fetal membranes intact and the presenting part at a one-plus station. Fetal heart tones were regular at a rate of 140.

The patient's last menstrual period was Oct. 13, 1939. Her previous labors had been normal with uneventful recovery. She was now having moderate pains every four minutes and was making good progress. At 7:50 P.M., two hours after admission, the membranes were bulging at the introitus and were ruptured. At this time twins were not suspected. At 8:30 P.M. the first twin was delivered but hung at the outlet. Vaginal examination revealed a second fetus in a transverse position, joined to the first by a stalk attached to the sternum. The union had been along the thorax, sternum, and lower abdomen, but most of this union had been sundered during the delivery of the first twin. There was complete evisceration of the liver and intestines. The stalk was severed and a version and extraction was done on the second twin. Both fetuses were stillborn. Because of hemorrhage, the placenta was removed manually. The placenta was single with one umbilical cord.

The patient was given 1 c.c. of pituitrin intramuscularly and 1 c.c. of ergotrate intravenously and had an uneventful puerperium, leaving the hospital on the ninth post-partum day.

*Necropsy Findings.*—(J. D. K.) The general form and contour of the monster are shown in Fig. 1. The relationship of the skeletal structures appeared normal as seen in an x-ray plate (Fig. 2). The twins were normally developed males externally; the larger (No. 1) weighed 2,250 Gm. and was 47½ cm. long; the smaller (No. 2) weighed 2,100 Gm. and was the same length. Each had normally developed upper and lower extremities. The scrotal sac of Twin 1 was empty, while that of Twin 2 contained the left testicle only.

The line of fusion of the twins began at the levels of the fourth rib of Twin 1 and the third rib of Twin 2. All the layers of tissue from the skin to the costal cartilage were involved at the upper end of the fusion, there being a common

black silk in each ligament, causing slight anteversion, thereby rendering impossible a pathologic anteversion; and by maintaining the portio within the environs of the receptaculum seminis, the normal or ideal position of the uterus is obtained.

A correspondingly higher attachment of the uterovesical fold of peritoneum to the body of the uterus with a running stitch of No. 1 chromic catgut augments the success of the operation and improves the support of the bladder. At the same time, correction of the accompanying prolapsed ovaries adds materially to the convenience and comfort of these women.

Our experience from the use of this operation warrants the conclusion that a retroverted uterus, so corrected, is ideally posed for the continuance of normal menstruation, for withstanding securely the force of intra-abdominal pressure, and for effecting normal and, more likely, a fruitful insemination.

#### SUMMARY

1. The successful treatment of 300 consecutive cases of retroversion of the uterus (nonpuerperal) by an uteroligamentopexy operation is described.

2. Various methods for the treatment of such retroversions with their shortcomings, including 4 to 15 per cent recurrences, have been reviewed.

3. This operation has for its intrinsic appeal simplicity of performance, anatomic soundness, physiologic adaptation, maintenance of normal relationships of the uterus and its ligaments to surrounding structures, recurrence of only 2 per cent and results ultimately satisfactory.

4. The timely correction of retroversion of the uterus (asymptomatic) in women who menstruate is recommended as a policy rational and prophylactic.

5. Use of this operation is commended to the profession with the hope that the resultant satisfaction may merit its increasing recognition.

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Pennell, Vernon: Removal of a Teratomatous "Twin," Brit. M. J. 2: 414, 1940.

A 6 by 4 by 3.5 inch lower lumbar and sacral mass was removed from a 5-week-old female. The mass had caused no difficulty at delivery. The mass was dissected free from the child under local anesthesia. A meningocele was found in the mass, this was opened, dissected free, and sutured. The child recovered in good condition. The mass consisted of much fat and connective tissue in addition to: (A) A smooth 2 by 1.5 inch cavity lined by cartilage or bone, containing: (1) A stomach which was connected to 7 inches of intestine leading to a blind cecum. (2) Two small buds, possibly liver and pancreas. (B) A tube (? esophagus) leading from the stomach to an external dimple on the mass. (C) Two small protuberances, possibly mandibular processes. All 3 layers were represented.

FRED L. ADAIR AND LESTER CRISMON.



Originating from the inferior aspect of the left ventricle close to the apex were the two rudimentary ventricles of Twin 2. These ventricles communicated with one another through a small defect and were attached to a common auricle by a fibrous cord. This common auricle had only a vestigial septum. The superior and inferior venae cavae entered the right half of the auricle. There was present also a similar transposition of the large vessels. The pulmonary ostium was stenosed. The left subclavian and common carotid arteries originated from a common short trunk. There was no ductus arteriosus.

There were two separate respiratory systems, the lungs of Twin 2 were three-lobed, and were half the size of those of its mate. Practically all of the liver was in Twin 1, except for a rudimentary lobe in the other to which it was attached.



Fig. 2.—Photograph of the x-ray showing the normal skeletal structure.

There was only one system of gall bladder and extrahepatic bile ducts. There were two pancreatic ducts. The gastrointestinal tracts were normal in both; spleens, pancreases and adrenals were normal. A single left testicle of Twin 1 was in the abdominal cavity; Twin 2 had two testicles, an abdominal testicle on the right, the other descended into the left half of the scrotum. The kidneys, ureters and urinary bladders were essentially normal in Twin 1, but in the second twin these organs presented some interesting anomalies which will be described in detail.

The kidneys were markedly reduced in size; the right one measured 18 by 18 by 5 mm. and the left one measured 26 by 12 by 13 mm. The right kidney, upon sectioning, contained a narrow rim of parenchyma up to 1 mm. in thickness. There was a marked dilatation of the renal pelvis and calyces, the pelvis being up to 26 mm. in circumference. In the right ureter the proximal 16 mm. was dilated up to 15 mm. and narrowed downward to a 2 mm. opening which extended into a huge

xiphoid. The skin ended about 1 cm. below the umbilicus and the remainder of the union was by a common peritoneal sac into which the liver bulged.

When the twins were separated, the defects formed were roughly oval shaped and measured 10.5 cm. in length and 11 cm. in greatest transverse diameter. In Twin 1 the manubrium appeared normal and the defect exposed the lower end of the body of the sternum, the xiphoid, and the ribs on both sides. The diaphragm was at the level of the sixth rib and had been fused to the diaphragm of the mate. In Twin 2 the defect commenced at the third rib. The sternum lacked a xiphoid process exposing the thoracic cavity. The diaphragm was likewise at the level of the sixth rib.



Fig. 1.—Photograph of the twins following birth. Note protrusion of large liver.

The organs of Twin 1 were, in general, better developed; most of the fused heart and most of the liver were present in this twin. Only those organs showing abnormalities will be described in detail.

A thymus gland was present, overlying the heart. There was a common pericardial sac and the hearts, which were each composed of three chambers, were fused to form a common circulation (Figs. 3 and 4). The heart of Twin 1 consisted of two large ventricles, the right larger than the left, and a single large auricle. The walls of the ventricles were hypertrophied. There was a widely patent tricuspid valve and a large interventricular septum defect. The superior and inferior venae cavae emptied normally into the auricle. There was a transposition of the large vessels with the aorta, arising from the right ventricle and the pulmonary artery arising from the left ventricle posterior to the aorta. The pulmonary ostium was stenosed. There was no ductus arteriosus. The vessels arising from the arch of the aorta showed no abnormalities. The mitral valve was missing.

sac 65 mm. in length and 43 mm. in transverse diameter. This sac, which occupied the middle two-thirds of the ureter, communicated with the distal end of the ureter through a small 1 mm. opening. The distal end of the ureter was 32 mm. long and was dilated up to 12 mm. in circumference. The ureterovesical orifice was patent. The left kidney contained more parenchyma than the right, and a cortex and medulla were distinguishable. The left ureter was 95 mm. long and its upper third was markedly dilated up to 31 mm. in circumference; near the distal end the circumference was reduced to 6 mm. The ureterovesical orifice was patent. The urinary bladder was dilated (Fig. 3).

No examination of the central nervous system was made.

#### SUMMARY

A case of a thoracopagus monster is presented, consisting of two male fetuses united at the thorax and upper abdomen. The union extended from the manubrium to about 1 cm. below the umbilicus. The common thorax contained 4 pleural cavities, a thymus, a single pericardium and a conjoined heart. A common diaphragm separated the thoracic structures from a single peritoneal cavity. There was a large fused liver with an additional rudimentary lobe, one gall bladder, and one system of bile ducts. The gastrointestinal tracts were normal. There were 3 testicles, 2 in the abdomen and 1 in the scrotum. The urinary tract of one twin presented several anomalies, namely a saccular dilatation of one ureter, with a megaloureter on the other side, and a marked hypoplasia of the kidneys. The two pulmonary systems presented no anomalies other than the small size and the presence of three lobes in each lung of one twin. The embryologic defects in the cardiovascular system were very pronounced. The hearts, one better developed than the other, consisted of 3 chambers each and were fused to form a common circulation. There was a transposition of the large vessels. The single umbilical cord attached to a common placenta contained 6 vessels, 2 umbilical veins and 4 arteries, normal in origin and distribution.

#### REFERENCES

- (1) Luckhardt, Arno B.: Surg., Gynec. & Obst. 72: No. 1, 116, 1941. (2) Ysander, Fredrik: Morphology and Morphogenesis of Human Thoracopagic Monsters, Upsala, 1924.

### AN UNUSUAL CASE OF HYDATIDIFORM MOLE

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THIS is a rare type of benign penetrating hydatidiform mole with spontaneous rupture of the uterus at the site of penetration into the uterine wall. It is of particular interest because the uterus was not enlarged out of proportion to the period of amenorrhea, as frequently seen in hydatid mole.

This case, like another seen recently with hydatid mole, was first admitted to the medical service because of a supposed cardiac decompensation associated with a beriberi type of heart.

M. L., a 35-year-old colored female, was admitted to the Surgical Service of St. Philip Hospital April 27, 1939, complaining of irregular vaginal bleeding. Five months before entering the hospital she had a spontaneous abortion with free hemorrhage, and had continued to hemorrhage at irregular intervals.

Examination revealed a well-developed and poorly nourished colored female; temperature was 100° F.; pulse, 120; respirations, 50; and blood pressure, 120/80. She had a bronchopneumonia involving only the right lower lobe, and was dyspneic and orthopneic. Pelvic examination revealed a tender mass in the right fornix,

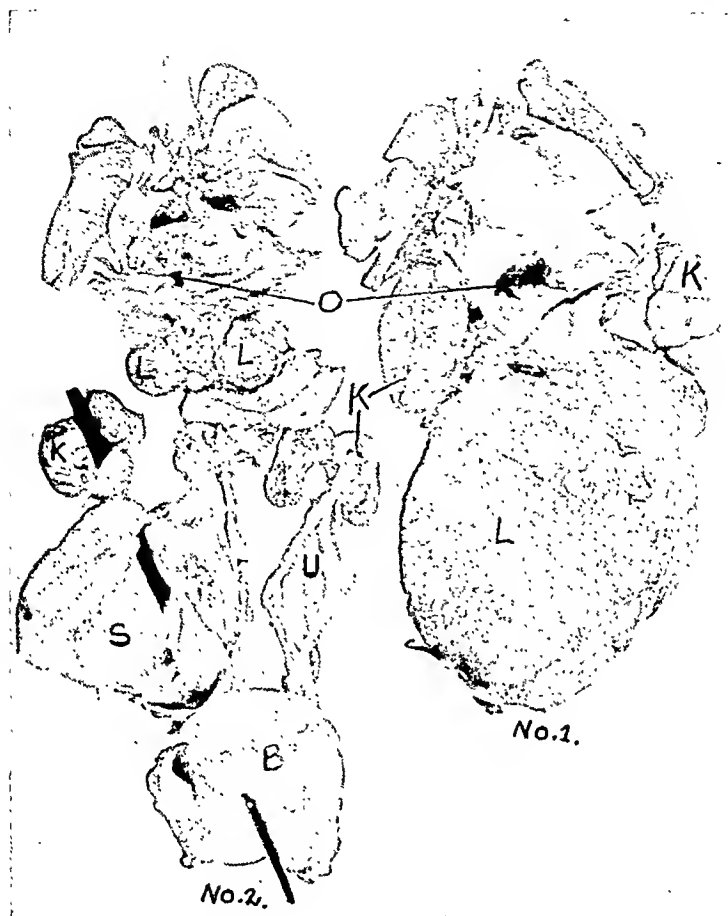


Fig. 3.—Photograph of the organs of both twins. *O*, shows the site of the fusion of both hearts; *L*, liver; *K*, kidneys; *S*, saccular outpouching of the right ureter; *B*, urinary bladder; *U*, megaloureter.



Fig. 4.—Photograph to show close-up view of the hearts of the twins. *O*, site of fusion of both hearts. Note the marked hypertrophy (*H*) of the ventricles in No. 1. *C*, the fibrous cord between the ventricles and the large auricle.

had not been in shock when seen in the emergency room, and examination prior to her admission to the obstetric ward had apparently precipitated the shock. She was given  $\frac{3}{4}$  gr. of morphine sulphate by hypodermic and 5 per cent glucose in normal saline, intravenously. Her blood pressure was then found to be 90 over 60, and her pulse was very rapid and weak. The heart rate and rhythm were regular; no murmurs were heard. Lungs were entirely clear. The abdomen was distended, very tense, and extremely tender throughout. A mass was outlined, extending out of the pelvis, to the level of the umbilicus in the midline. Pelvic examination revealed the entire right fornix bulging with a doughy mass which was extremely tender. This mass extended a little to the left of the midline, but the left fornix seemed normal. The cervix could not be made out, either on palpation or speculum examination. The mass in the right fornix seemed continuous with the mass in the lower abdomen. There was no blood or hydatid tissue in the vagina.

Laboratory studies revealed red cells 3,600,000, hemoglobin 58 per cent, white cells 18,250, polymorphonuclear leucocytes 77 per cent, and lymphocytes 23 per cent. A catheterized specimen of urine showed albumin 2-plus and 15 to 20 pus cells per high power field. The blood count was repeated at 2:30 P.M., two hours after the first count. It showed red blood cells 2,600,000, hemoglobin 28 per cent, and white blood cells 15,100. The urine was positive for acetone.

A donor was obtained, and the patient taken to the operating room for an exploratory laparotomy at 4:00 P.M. She was given oxygen, nitrous oxide, and ether for anesthesia, and the abdomen was opened through a right paramedian incision. Upon opening the peritoneum, a large amount of dark blood escaped under some pressure. The peritoneal cavity was found to contain both fresh and old blood clots, a total of probably 1,500 c.c. The uterus extended up to the level of the umbilicus. There were several small fibroids in the fundus and the anterior surface of the uterus. The fibroids varied in size from that of a marble to a walnut. A rupture 5 to 6 cm. in diameter, and more or less circular, was found on the posterior surface of the uterus. The uterus was lifted from the abdominal cavity, and a large amount of hydatidiform mole escaped from both the uterine and the abdominal cavities. There were several areas in the uterus which were apparently infiltrated with the same diseased process, which had almost ruptured. As much of the mole and blood as possible were removed from the abdominal cavity. The patient was bleeding freely at the site of the rupture, and a supravaginal hysterectomy was done. It was found that the cervical stump, uterine wall, broad ligament on the right, and possibly the ovary on the right were all infiltrated with the hydatid mole. The cervical stump was necrotic and friable. It was closed and peritonized.

The patient was transfused during the operation, receiving 550 c.c. of blood by citrate method. Her condition was very poor, and she was hardly breathing when returned to the ward. We were unable to obtain her pulse or blood pressure during most of the operation.

Upon returning to the ward, nasal oxygen was started, at the rate of 3 liters per minute, and increased to 6 or 7 liters per minute. She was transfused again four hours after operation, receiving 550 c.c. of blood by citrate method. Her blood pressure came up very slowly to systolic 120 and diastolic 80, and remained at this level for about six hours. Later, the blood pressure dropped to systolic 50 and diastolic 40, and remained at this level even after active treatment for shock. Six hours after operation her temperature was 103.6° F., and remained at that level. She died at 10:30 A.M., April 28, about eighteen hours postoperative.

*Pathologic Report.*—The reconstruction of the surgical and autopsy specimen showed a large mass of hydatidiform mole, measuring approximately 9 cm. in diameter, situated in the right broad ligament and pelvic tissues. The mass was apparently in direct continuity with the lumen of the uterus through an opening in the right lateral wall of the cervix, approximately at the level of the amputation. The pelvic mass of hydatiform mole was well encapsulated and did not penetrate into the tube, ovary, or ureter. It was composed of irregular grapelike vesicles which varied extremely in size. Necrosis and hemorrhage were seen close to the hilus of the right ovary and near the site of amputation of the uterus.

A frontal section through the midportion of the uterus revealed that the latter was collapsed, but still showed hydatiform mole in its lumen which at various

which extended down into the cul-de-sac and was fairly firm. The uterus was not definitely outlined, and the size of the mass was not noted. It was thought to be a tuboovarian abscess.

Laboratory studies revealed red blood cells 2,300,000, hemoglobin 28 per cent, white blood cells 5,900, polymorphonuclear leucocytes 76 per cent. Urinalysis was negative except for one-plus albumin and 20 to 30 pus cells per high power field.

The patient was transferred to the medical service for treatment of the pneumonia. On the medical service, dyspnea was thought to be due to cardiac decompensation with a beriberi type of heart. Blood chemistry studies revealed a moderate nitrogen retention, with nonprotein-nitrogen 45 mg., and a low total protein of 5.4 Gm. She was digitalized and put on restricted fluids and a low caloric, high protein, high vitamin diet. She was transfused once while she was

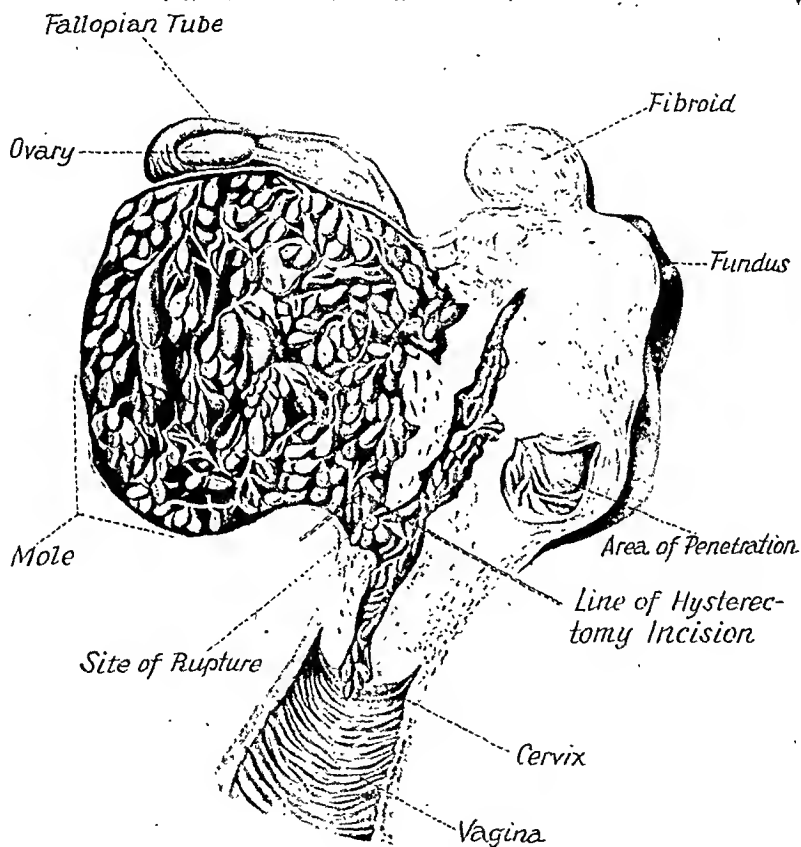


Fig. 1.—Drawing of reconstructed specimen.

on the medical service, receiving 500 c.c. of blood by citrate method, and showed a remarkable amount of improvement. She signed a release and left the hospital against advice, May 17, 1939. Her last blood examination showed red blood cells 1,800,000, and hemoglobin 34 per cent.

This patient was next seen on July 10, 1939, when she was admitted to the Obstetrical Service of St. Philip Hospital with a diagnosis of ruptured ectopic pregnancy. At this admission, a history was obtained that she fell on her abdomen about three weeks prior to admission, and had complained of moderately severe pain and weakness since that time. Her family doctor had repeatedly advised hospitalization, but she refused to take his advice.

Examination on admission to the obstetric ward revealed a well-developed, but poorly nourished, colored female, obviously in shock. She was very apprehensive, cold and clammy, and we were unable to obtain her pulse or blood pressure. She

In our histologic description, we mention a necrosis of the connective tissue surrounding the intravenously penetrating villi. This could be interpreted as the effect of a destructive character of the mole. However, every normal placenta is just as destructive. It produces fibrinoid necrosis known as zone of Nitabuch and even in the depth of the uterine wall coagulation necrosis can be observed about the villi which penetrate into the marginal veins or deeper into the veins of the muscular wall. The necrosis of uterine tissue in our case is not fibrinoid in character, but mere coagulation of the connective tissue matrix associated with loss of nuclei. This, however, is essentially identical with changes seen under normal conditions.

## REFERENCES

- Mathieu, Albert*: International Abstr. Surg. 68: 181, 1939. *Meyer, Robert*: Henke and Lubarsch Handb. d. Spec. Pathol. Anat. u. Histol. 7: p. 700, 1937. *Mathieu, Albert*: AM. J. OBST. & GYN. 37: 654, 1939.

## SPONTANEOUS PERIRENAL HEMATOMA AS A POST-PARTUM COMPLICATION

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SPONTANEOUS perirenal hematoma has been previously described as a relatively uncommon entity. Courroy<sup>1</sup> reported 34 cases of aneurysm of the renal artery with hematoma, and additions were made to the literature by Drs. Meyer and Singer in 1927.<sup>2</sup>

We wish to report a case which followed a pregnancy. Hypertension, tuberculous or syphilitic infections, mycotic emboli, and blood dyscrasias played no role in the etiology. Trauma, however, is a questionable factor. A mass was observed after delivery, but it was only after a fall that this became more apparent with symptoms. The following case is reported because of its relative infrequency, and particularly because of its association as a post-partum complication:

I. W., colored female, aged 24 years, was admitted to the Cook County Hospital on Sept. 8, 1938, with a history of (1) pain in the abdomen for eighteen days, (2) mass in the right upper quadrant for seventeen days, (3) anorexia for one week, and (4) fever and sweats for four days.

The patient was delivered of a premature eight-month infant on Aug. 19, 1938, after an uneventful ante-partum course. Three days after delivery she noted a swelling in the right upper quadrant. Later that day she noted that the swelling became painful. This was considered of little significance, and she was discharged from the hospital on Aug. 27, 1938, although the mass was still present.

Four days after her dismissal, she tripped over a dog and fell. Soon after this incident she noted pain in the right shoulder, and the right upper quadrant pain, of which she had previously complained, became more severe. Four days prior to her readmission she began having chills and sweats. During the preceding two days she vomited at least twice daily.

Her menstrual history was normal, and the last period occurred Jan. 15, 1938. Her first pregnancy was a female infant delivered at eight months; second, a male at seven months, died at birth; third, a male at 8 months, living and well.

On physical examination her blood pressure was 100/80; temperature, 100.6° F.; and pulse, 110. She had a slight icteric tinge to her skin. Head, mouth, nose, throat, neck, lungs, and heart were all normal.

The abdomen was asymmetrically distended with a visible mass below the right anterior costal region and flank, which was about 10 cm. in diameter and very tender. The muscles overlying were quite tense. There was also marked tenderness in the right flank. The liver edge could be felt moving with respirations. Peristalsis was heard in the lower abdomen and was slightly obstructive in character.

On pelvic examination, the cervix was soft, and fundus soft and movable. Motion caused pain in the upper abdomen. The adnexa were negative, except

points penetrated into the thick wall of the uterus, disclosing itself in form of smaller and larger cysts filled with thin mucoid material. At several points these cysts appeared underneath the serosa of the uterus.

Other gross findings were not pertinent. In view, however, of the disturbances of cardiac function, it must be mentioned that grossly and microscopically the heart was free from pathologic changes. Vacuolic disorder of myocardial fibers could not be demonstrated.

It should be mentioned that both ovaries were free from lutein cysts. However, the right ovary was adherent to the tumor mass and hemorrhage, necrosis, and a silk ligature were found at this point. A corpus luteum cyst previously present may have been destroyed and become unrecognizable. We can, therefore, not be absolutely sure that no corpus luteum cyst was present.

Sections through various portions of the hydatiform mole, outside and inside the wall of the uterus and through the endometrium, revealed the typical picture of a benign hydatiform mole characterized by large villi, the stroma of which was almost entirely free from vessels, edematous, with evidence of mucoid degeneration. In the center of many of the villi was found complete liquefaction necrosis of the connective tissue stroma. Most of the villi were covered by syncytial elements only, but occasionally both Langerhans' and syncytial elements were found. The Langerhans' cells, though scarce, were equal in size, cuboidal in shape with normally structured nucleus. The syncytial elements were those found in normal mature placental tissue with dense dark-stained nuclei, frequently forming buds, but there was no evidence of regressive changes, nor undue proliferation, nor independent growth of the chorionic-epithelial elements. The villi were seen within the wall of the uterus, but everywhere within pre-formed spaces lined by endothelial cells. These spaces were taken to be venous sinuses. It is of interest that the tissue immediately surrounding the sinuses revealed regressive changes resulting in almost complete necrosis of the connective tissue and the adjacent muscle bundles. This necrosis lacked inflammatory reaction, but was taken to be ante mortem, because it was found nowhere except in the immediate vicinity of such sinuses which were filled with chorionic villi.

#### COMMENT

The case is classified as one of the so-called penetrating hydatiform moles, which is sometimes referred to as "destructive hydatiform mole." Though limited penetration of the uterine wall by hydatiform mole is commonly found, massive growth in extrauterine tissues is apparently very rare.

Mathieu in his last collective review mentions 10 cases of uterine rupture due to penetrating hydatiform mole. It is difficult, however, to estimate the number of reported cases, because some of them have been misinterpreted as chorion epitheliomas. However, if the morphologic criteria laid down for the recognition of malignancy in general and for chorion epitheliomas in particular, are taken into consideration, our case offers exceptionally little difficulties in classifying it as a strictly benign growth.

The first and foremost histologic criterion of malignancy, namely, the independent growth of chorionic-epithelial elements is absent in our case. With few exceptions where groups of epithelial elements adhere to the inner lining of the uterine sinuses, the growth is strictly confined to the surface of the villi. Detached growth on the surface of blood clots is not encountered. The chorionic-epithelial elements do not infiltrate the stroma of chorionic villi. They show no autonomic proliferation exceeding the normal ramification of villi.

There is furthermore no definite anaplasia recognizable. It is, of course, not easy to apply our usual concept of the morphologic appearance of anaplastic cells to chorionic-epithelial elements. In this particular type of cells our criteria are not reliable if anaplasia is taken to be an indication of malignancy. We can, however, state that the chorionic epithelial cells in our case do not vary more in shape, size and staining effect than those seen in normal placentas. Mitotic figures are absent. Furthermore, the stroma of the villi does not actively participate in the growth, but merely reveals regressive changes.

Metastases have not occurred, the cell emboli in lung capillaries being regarded as normal.



## CARCINOMA OF THE FEMALE URETHRA

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SEVERAL reviews of the literature on carcinoma of the female urethra have been made in recent years. Counseller and Paterson,<sup>1</sup> in 1933, found a total of 124 cases and added 12 of their own. Menville<sup>2</sup> added 10 cases, bringing the total in 1935 to 149. Sparks and Parsons<sup>3</sup> reported a case in 1937 and tabulated the literature, making a total of 168.

Every attempt must be made to differentiate primary urethral carcinoma from secondary carcinoma arising in the labia majora or minora, vestibule, Bartholin's gland, clitoris, or vagina. Within the urethra the usual lesions which are to be differentiated are prolapse of the urethral mucosa, caruncle, fibroma, and sarcoma.

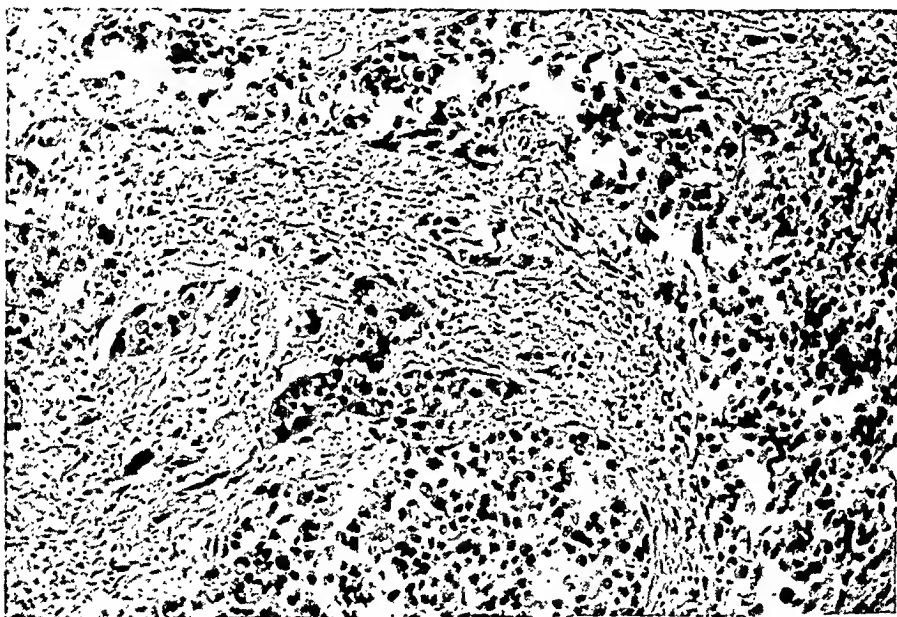


Fig. 1.—Squamous cell carcinoma invading the thin-walled cavernous spaces in the wall of the urethra.  $\times 175$ .

A housewife, 57 years of age, entered the Grant Hospital of Chicago on June 6, 1938. She complained of genital bleeding and pelvic pain. A small palpable red mass had been present at the urethral orifice for three weeks. The menopause occurred eight years before. She had been married for eight years and had no children. An examination revealed a small, elevated, red ulcerated mass, involving the left lip of the meatus. Vaginal examination showed fixation of the entire urethra. A hard mass could be felt, and this gradually narrowed and disappeared at the bladder neck. The cervix uteri was not involved. No inguinal adenopathy was noted.

A suprapubic cystotomy was performed on June 10, 1938. The region of the bladder neck appeared indurated by tumor tissue. She left the hospital on June 29, 1938, and returned for roentgen ray treatments during July, August, and September. She was readmitted to the hospital on Oct. 7, 1938. At this time she

that pressure on the right side caused pain in the right flank. Pressure on the abdominal mass did not move the cervix.

The blood showed 2,350,000 erythrocytes, 50 per cent hemoglobin, 10,500 leucocytes, and the differential showed 74 per cent polymorphonuclears, 24 per cent lymphocytes, and 2 per cent monocytes. The blood Wassermann was negative.

The impression was: (1) liver abscess with hepatitis, (2) subhepatic abscess, and (3) high lying ovarian cyst with hemorrhage. Hydronephrosis and an echynococcus cyst were ruled out.

Conservative treatment, with bed rest, morphine, intravenous dextrose and saline, and blood transfusions, was instituted.

A flat plate of the abdomen revealed a soft tissue mass in the painful area and a high diaphragm with restricted movements. The bleeding time was 4 minutes 50 seconds.

She was cystoscoped but no pathology was noted. Ureteral catheters passed readily. Because of the mass, retrograde pyelograms were made. These revealed a normal right kidney pelvis, except for its position which was to the left of the midline at the level of the fourth lumbar vertebra. No deformity was noted on the left side.

A diagnosis of a retroperitoneal cyst was made and on Sept. 17, 1938, an exploratory operation was done by Dr. R. W. McNealy through a right paramedian incision. Here a large perirenal hemorrhagic cyst was found lying in the retroperitoneal space in the region of the upper pole of the right kidney. A diagnostic aspiration of 10 c.c. of hemorrhagic fluid was made. Iodoform gauze was packed between the cyst wall and the parietal peritoneum, so as to marsupialize the anterior wall of the mass.

On Sept. 24, 1938, she was re-operated upon and 2,500 to 3,000 c.c. of old blood and serum were removed from the cyst. Near the base, organized clots were obtained and after their removal bright red blood appeared. The cavity was then packed with two ten-yard uterine gauze rolls.

During the following week, the patient's course was very septic with chills, fever, and jaundice. On the eleventh postoperative day her course leveled off to normal.

After rehabilitation she went to surgery on Oct. 11, 1938, for a third time. On this occasion she was operated upon through a right lumbar incision. A large cystic mass originating from the upper medial pole of the right kidney or adrenal was found. The contents were foul smelling and suggestive of protein digested tissue. The cystic mass, right kidney, and adrenal were removed, and the wound closed, with the insertion of two Penrose drains.

On the first postoperative day her fluid intake was 3,550 c.c. and the urinary output 700 c.c. On the second postoperative day, the intake was 3,850 c.c. and the output 750 c.c. Her course from that time on was uneventful, and she was discharged from the hospital on Nov. 5, 1938.

*Pathology.*—Kidney 10 by 5 by 3.4 cm. Cortex stripped with ease and was pale tan gray. Attached to the anterior medial portion in the region of the pelvis was a stalk 6.5 by 2.5 by 0.5 cm., bearing a mass 25 by 15 by 5 cm. This had previously been opened.

*Microscopic Findings.*—Section of the cystic mass revealed dense edematous connective tissue wall which was very vascular and infiltrated by round cells. Lumina of the vessels were obliterated by blood clots, and there was marked proliferation of the intima. There was atrophic adrenal tissue encapsulated by proliferating scar tissue. The inner lining was of fibrin network with erythrocytes and a necrotic membrane with clouds of bacteria. The picture was that of an old organized hematoma or aneurysm.

On Oct. 13, 1939, one year later, she was delivered of a normal 8-pound male infant after an uneventful pregnancy.

#### REFERENCES

- (1) Conroy, M. J.: *Ann. Surg.* 78: 628, 1923. (2) Meyer, Karl A., and Singer, Harry: *Surg., Gynec. & Obst.* 45: 300, 1927.

was 120 systolic and 80 diastolic. The breasts were moderate in size; no masses could be found. Abdominal examination revealed no masses, no herniations, and no points of tenderness. The abdominal musculature was rather poor. The liver, both kidneys, and spleen could not be felt.

Upon examination of the pelvis, a markedly relaxed outlet was found, with a fairly large cystocele and a moderate rectocele. The cervix, which was badly eroded, lacerated, and hypertrophied, protruded almost to the outlet. The uterus was in second-degree retroversion, soft, irregular, but normal in size for a multipara. Both adnexal regions were negative.

X-ray examination of the chest showed a slight tuberculous fibroid infiltration of apices of both lungs, with thickening of the pleura at the right base.

*Diagnosis.*—Cystocele; rectocele; first-degree prolapse of uterus; chronic endocervicitis with erosion, laceration, and hypertrophy.

*Operation.*—On March 7, 1936, a vaginal hysterectomy was done under gas ether anesthesia. A large gauze pack was used as a drain in the posterior cul-de-sac.

The course in the hospital was febrile. The gauze pack was removed on the fourth day following operation, but the patient had a temperature elevation rising to 102° F. throughout the first two weeks of the postoperative course. At one time a questionable mass was felt in the cul-de-sac, but this gradually subsided, as did the temperature elevation. The patient was discharged as cured on the twenty-fourth postoperative day.

On April 20, 1936, the patient returned for her first postoperative examination. Upon examination of the vaginal vault, an elongated granulating mass was seen protruding from its apex. The patient had no complaints, no vaginal bleeding, and no pain. A moderate amount of vaginal discharge was present, however. The primary result of the operation was good. The mass was avulsed and the base cauterized.

Microscopic examination of the tissue received revealed it to be a Fallopian tube.

## IMPERFORATE HYMEN BEFORE THE MENARCHE WITH MUCOCOLPOS AND MUCOMETRIUM\*

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**I**MPERFORATE HYMEN with hematocolpos is not rare. In 1939, Tompkins<sup>1</sup> reviewed 113 cases in the literature and added 5 more. Imperforate hymen before the menarche associated with an accumulation of mucus in the vagina and uterus probably has not been previously reported, and in view of its uniqueness this case is here recorded.

The patient was a 12-year-old twin Jewish girl who was admitted to the West Baltimore General Hospital, April 30, 1939. The patient had experienced mild right lower quadrant and midabdominal discomfort but had never had any pain. Bowel movements had been regular and there had been no emesis. During a routine examination, a mass was found in the lower abdomen. The child's mother had died from Hodgkin's disease. The child had never menstruated.

The patient was a well-developed and well-nourished girl. She was cheerful, intelligent, and cooperative. There was a symmetrical protrusion of the lower abdomen from the umbilicus downward. On palpation, a soft mass was felt, extending from the pelvis to the umbilicus. The mass was symmetrical and a questionable nodule was felt just to the right of the umbilicus. Rectal examination showed that the mass was smooth walled and in the midline. The pubic hair was well developed. Between the labia there was a pink, white spherical protrusion; and this was more prominent when the patient strained. The leucocyte count was 10,000 with 80

\*This case is from the practice of Dr. S. H. Barranco.

complained of vaginal bleeding and blockage of the indwelling catheter. The red blood count was 3,200,000 cells per c.mm. and the white blood count was 10,700 cells per c.mm. The nonprotein nitrogen was 91 mg. and the uric acid 8 mg. per 100 c.c. of blood. She died on Oct. 12, 1938.

At autopsy many blood clots could be expressed from the bladder through the cystotomy opening. The urinary meatus admitted a small probe. The entire length of the urethra was invaded by tumor tissue, the greatest thickness being near the meatus. The greatest thickness of the wall was 30 mm. on the left side and 12 mm. on the right side. The labia majora and minora were atrophic. The anterior wall of the vagina, trigone of the bladder, and anterior wall of the cervix were infiltrated by tumor tissue. A wooden applicator was inserted easily into each urethral orifice. The ureters were dilated on both sides. At the ureteropelvic junction, they measured 22 mm. in diameter. The pelvis and calices of the left kidney were moderately dilated. Both lungs showed extensive metastatic tumor nodules, measuring up to  $2\frac{1}{2}$  cm. in diameter.

Microscopic sections taken through the thickened urethra showed infiltrations of squamous cell carcinoma, many of the tumor cells being within the wide thin-walled venous channels. Slight hornification of the tumor cells was found in some areas. The metastases in the lung had a similar structure but without any traces of hornification.

#### SUMMARY

The infiltrating type of squamous cell carcinoma of the female urethra, if not recognized very early in the course of the disease, offers a very poor prognosis. Metastases can readily occur by way of the venous channels in the wall of the urethra.

#### REFERENCES

- (1) *Counseller, V. S., and Paterson, S. J.*: J. Urol. 29: 587, 1933. (2) *Menville, J. G.*: Surg., Gynec. & Obst. 61: 229, 1935. (3) *Sparks, T. P., Jr., and Parsons, W. H.*: Urol. & Cutan. Rev. 41: 157, 1937.

## PROLAPSE OF A FALLOPIAN TUBE FOLLOWING VAGINAL HYSTERECTOMY

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BOWER, Pearce, and Conway, in the December, 1940, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, report a case of prolapse of Fallopian tubes with vaginal bleeding following vaginal hysterectomy. A similar incident occurred in one of our cases of vaginal hysterectomy, although the patient had no symptoms.

This patient, a 40-year-old married housewife, was referred to the hospital Jan. 23, 1936, for treatment of a badly eroded and hypertrophied cervix. Her only complaint was that of a gnawing pain in the left lower quadrant, especially noticeable during the previous two months. There were no associated urinary, gastrointestinal or menstrual complaints.

The systemic history was entirely negative. Catamenia began at 13 years of age, occurred regularly every four weeks, lasting from four to five days, except that in the last few months there had been some slight irregularity. The last menstrual period was Jan. 3, 1936. At no time had the patient experienced metrorrhagia, menorrhagia, or dysmenorrhea. She had been married nineteen years, having had six normal deliveries. The oldest child was eighteen years and the youngest, two years of age.

The physical examination revealed a rather thin white female, in no apparent acute distress. The patient was rather pale but presented no gross abnormalities. The secondary sex characteristics were well developed. The somatic examination was negative except for a few equivocal signs in the upper chest. Blood pressure

be palpated. On abdominal palpation, the lowermost fetus was diagnosed as a right transverse, but the upper fetus could not be definitely outlined. Two fetal hearts of unequal rate were heard, being 140 and 160, respectively. At 3 P.M. an x-ray was taken, which revealed the lower fetus lying with the head in the right flank and the upper fetus also transverse, with its head under the spleen. At 4 P.M. she was taken to the operating room for a vaginal examination. The contractions, at this time, were every six minutes and of rather poor quality. On vaginal examination, the spinal column of the fetus was found directly across the cervix, which was two fingers dilated, the membranes being ruptured. It was felt that since the chances of her reaching full cervical dilatation spontaneously, in view of the presentation with ruptured membranes, were small, interference was indicated. A



Fig. 1.—X-ray showing the lower fetus to be in a right transverse and the upper one to be in a left transverse position. The outlines of the heads has been accentuated.

foot was not brought down, as it was felt that there might be difficulty in bringing the lowermost body into a vertical position, due to the position of the upper fetus and also the danger of a prolapsed cord. Consequently, a No. 5 Voorhee's bag was inserted without any difficulty, and the patient was returned to the labor room. Three hours later, the contractions had increased in frequency to every four minutes and the bag, on rectal examination, was almost halfway through the cervix, which was a little over three fingers' dilated. No weight was used on the bag. At 9 A.M., the following morning, sixteen hours after the bag was inserted, it was expelled spontaneously, and she was immediately taken to the delivery room. The cervix was found fully dilated and the presenting part was still the middorsal spine of the fetus. The body was slightly rotated on its long axis, so that the feet could be more easily reached, and the version was slowly completed, followed by the extraction of

per cent polymorphonuclear cells. The urinalysis and blood Wassermann were negative. Flat roentgenogram of the abdomen revealed a large mass extending up to the level of the third lumbar vertebra.

The patient was taken to the operating room on the third day after admission, and under evipal anesthesia an incision was made in the hymen. About 2 quarts of milky chylelike fluid escaped. The cervix was grasped with a tenaculum and a uterine sound was inserted  $1\frac{1}{2}$  inches into the uterus. A uterine pack was inserted loosely into the vagina. The vaginal pack was removed the following day and the patient was discharged.

The patient was seen by Dr. Barranco thirteen days after discharge, and at that time, vaginal examination revealed a slight mucoid discharge and an edematous cervix. Two months later the cervix was normal and the discharge was less. Hot potassium permanganate douches were advised. The patient was an identical twin, and her sister was examined at the time of operation and found to have a perforate hymen. This sister began to menstruate July 24, 1939, and the patient began to menstruate Oct. 10, 1939 (about five months following operation). The child's menstrual periods have been regular and there has been no dysmenorrhea. When the patient was examined fifteen months after operation, an adequate hymenal opening was found to be present, and at that time she weighed 105 pounds, having gained 15 pounds since operation.

A search of the literature reveals no similar case. We have compounded the terms mucocolpos and mucometrium which seem aptly to describe this condition. It is possible that a mucocolpos and mucometrium may exist before the menarche, and the onset of the menses may convert the mucoid fluid into a bloody one. This may be an explanation of some of the cases in which, with the history showing the patient to have been menstruating only one to two months, hymenectomy results in the evacuation of 500 to 1,000 c.c. of bloody fluid.\*

#### REFERENCE

(1) *Tompkins, P.*: J. A. M. A. 113: 913, 1939.

613 GREENLEAF BUILDING

## TWIN TRANSVERSE PRESENTATION

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THE extreme rarity of twin transverse presentation makes this report of interest.

Mrs. P. C., an Italian woman, aged 32 years, was first seen in her sixth month of gestation on October 1. Her last menstrual period started on April 10, making the expected date, December 17. The general physical examination was essentially negative. Ten years ago, she was delivered at full term with low forceps, following an eighteen-hour labor, of a male child, weighing 10 pounds. The puerperium was uneventful. She became pregnant again, one year ago, which terminated in a complete spontaneous abortion at two months, with an uneventful recovery. Her pelvic measurements were ample in all diameters. She weighed 170 pounds. Abdominal examination at this time showed a uterus one-third of the way above the umbilicus and palpation was inconclusive. Pregnancy continued uneventfully up to the seventh month, when she developed a right-sided pyelitis, which was cleared up completely under Mandelic acid and ammonium chloride therapy. At the eighth month the uterus measured 39 cm. from the top of the symphysis, and twins were diagnosed. She started labor on December 21 which was eleven days past the calculated time. She was admitted to the Israel Zion Hospital the same date at twelve o'clock noon with contractions at seven- to ten-minute intervals, lasting thirty seconds. Labor had started six hours previously with the spontaneous rupture of the membranes. Rectal examination revealed an empty pelvis and the cervix could not

\*See abstract at bottom of page 67 of this issue.—Editors.



Fig. 1.—Section of biopsy, showing early squamous cell carcinoma of the cervix.

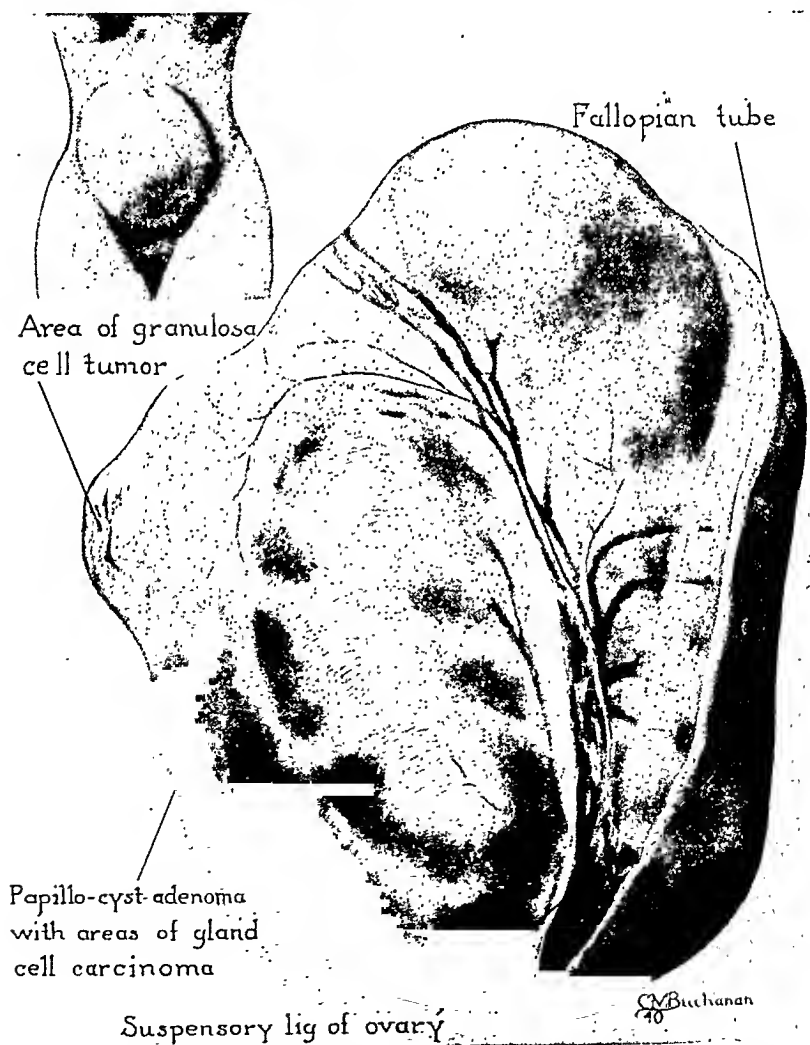


Fig. 2.—Encapsulated cystic tumor before sectioning.

living 5 pound 6 ounce male baby. An interval of ten minutes permitted the uterus to regain its tone, when the second bag of waters was ruptured. This fetus was found to lie with its lower right ribs towards the cervix, the head being in the left upper flank. The feet were brought down through the cervix and version and extraction resulted in a living 5 pound 4 ounce female child. No episiotomy was necessary as the pelvic floor was markedly relaxed. The placenta was expressed with a modified Credé method ten minutes later. There were two placentas separated by a narrow membranous cleft with separate amnions and chorions. The puerperium was uneventful, and she left the hospital in ten days with both babies.

## DOUBLE PRIMARY OVARIAN MALIGNANCY

### GRANULOSA CELL TUMOR OF THE OVARY FOLLOWING RADIUM THERAPY FOR CERVICAL CARCINOMA WITH PAPILLARY CYSTADENOMA OF THE SAME OVARY

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MULTIPLE malignancies are no longer considered a clinical rarity. It has been estimated by Warren and Gates<sup>1</sup> that 1.84 per cent of patients harboring malignant neoplasms have more than one primary malignant lesion. These tumors are usually found in the same organ or in organs of the same system or symmetrical systems, but may occur in different systems. Whereas multiple malignancies of the skin, large intestine, or stomach are observed relatively frequently, only a few cases of more than one malignant growth in the same ovary have been recorded. Major<sup>2</sup> in an extensive review of the literature in 1918 was able to find only three examples: one reported by Rahl-Ruckhardt,<sup>3</sup> a case of carcinoma and sarcoma of the ovary; Lippmann's,<sup>4</sup> a case of carcinoma sarcomatodes of the ovary; and Rothacker's<sup>5</sup> case of carcinoma and sarcoma of the ovary. In 1934, Hughes<sup>6</sup> cited one instance of multiple ovarian malignancy, an adenocarcinoma and leiomyosarcoma of the ovary. Primarily because so few of these cases have been reported, the following case is presented.

#### REPORT OF A CASE

Mrs. W. F., aged 71 years, was admitted to Touro Infirmary, July 20, 1940, because of a greatly enlarged abdomen, weakness, and a loss of five pounds in weight. She did not complain at any time of uterine bleeding.

Twelve years before, on Sept. 25, 1928, she was seen for the first time, complaining of external vaginal pruritus of four months' duration and of a loss of 5 pounds in weight during the preceding three months. She had had five normal deliveries and one miscarriage. The menopause had occurred at the age of 51 years. Examination revealed a profuse pus discharge from the cervix. A diagnosis of chronic purulent discharge from the cavity of the uterus was made. Dilatation and curettage on Oct. 24, 1928, disclosed early squamous cell carcinoma of the cervix (Fig. 1). The patient was given 50 mg. of radium for twenty-four hours and 100 mg. for twenty-four hours or a total dosage of 3,600 mg. hr. She has been seen intermittently since that time. In 1936, a notation was made that the lesion had completely healed and that the uterus and adnexa were normal. In July, 1938, and again in August, 1939, pelvic examination showed the adnexa and cervix to be normal, the canal patulous, and the uterus small and in an anteverted position.

Pelvic examination on her last visit, July 18, 1940, revealed a normal cervix, no bloody discharge on probing the cervical canal and a greatly enlarged abdomen.



## REFERENCES

- (1) Warren, S., and Gates, O.: *Am. J. Cancer* 16 (pt. 1): 1358, 1932. (2) Major, R. H.: *Bull. Johns Hopkins Hosp.* 29: 223, 1918. (3) Rahl-Ruckhardt: Cited by Major.<sup>2</sup> (4) Lippmann, H.: *Ztschr. f. Krebsforsch.* 3: 293, 1905. (5) Rothacker, A.: *Ibid.* 12: 39, 1913. (6) Bugher, J. C.: *Am. J. Cancer* 21: 809, 1934. (7) von Kahlen, C.: *Zentralbl. f. allg. Path.* 6: 257, 1895. (8) von Werdt, F.: *Beitr. z. path. Anat.* 59: 453, 1914. (9) Te Linde, R. W.: *AM. J. OBST. & GYN.* 20: 552, 1930. (10) Bland, P. B., and Goldstein, L.: *Surg., Gynec. & Obst.* 61: 250, 1935. (11) Pratt, F. B.: *J. Obst. & Gynaec. Brit. Emp.* 44: 880, 1937. (12) Schulze, Margaret: *West. J. Surg.* 47: 114, 1939.

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## SEVERE MATERNAL TRAUMA IN EARLY PREGNANCY

## CONGENITAL AMPUTATIONS IN THE INFANT AT TERM

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THE special interest of the present case lies in the occurrence of major trauma at about the close of the first trimester of pregnancy, and the delivery at term of an infant presenting multiple congenital amputations. A causal relationship between the maternal injury and the fetal defects cannot be established, but since the possibility is not absolutely excluded, the potential medicolegal aspects of this and similar cases are deserving of note.

Mrs. E. L. D., white, aged 29 years, was found in an unconscious state on a highway Jan. 6, 1940. She was still unconscious when brought by the police to the accident room at Charity Hospital. The patient exhibited an extreme degree of shock, blood pressure being 50/20. Fractures, multiple lacerations, contusions, and abrasions were present, and there was a partial avulsion of the scalp. A catheterized specimen revealed gross hematuria. The patient responded to shock treatment, the blood pressure rising to 100-120/50-70. She was given a double dose of mixed serum.

Upon regaining consciousness the patient explained that she had been walking alone on the highway. Though she could recall nothing of the accident, the circumstances point to her having been struck by an automobile. She was three months pregnant; the last menstrual period began about October 5. Her only previous pregnancy was normal, with delivery at full term about two years before.

X-rays were made, with the following findings:

1. Fracture of the right acromial process.
2. Fractures of the left pelvis at the junction of the ascending pubic ramus and the ischium and at the junction of the descending ramus and ischium.
3. Fracture of the sacrum, with no displacement.
4. Compound comminuted fractures of the lower halves of the right tibia and fibula, with overriding.
5. Fracture of the right parietal (from which the patient complained of persistent headache and diplopia).

Subsequent urinalyses showed no blood. A second double dose of mixed serum was given on January 7.

Appropriate fracture treatment was instituted. Osteomyelitis developed in the right leg about ten days after admission, in treatment of which a cast was applied and changed from time to time. She ran a low grade fever for three weeks. Quickening was first noted on February 15.

Fluid waves were definitely present. Whether this was free fluid in the abdomen or an encapsulated mass was not determined at the time of examination. The chest was normal.

A diagnosis of malignancy of the ovary was made. Upon opening the abdomen, a large, multilocular cyst of the right ovary was encountered (Fig. 2). Exploration showed that the cyst had not ruptured and that there was no free fluid in the peritoneal cavity. The entire cyst was easily delivered from the abdominal cavity and removed intact. The tumor was well encapsulated and measured 22 cm. by 16 cm. by 11 cm. There were no cystic changes in the left ovary, but it was larger than would be expected for a woman of that age. Both ovaries and tubes were removed. The uterus was not removed because of the patient's age, because she had had previous radiation to the cervix and because the mass was well encapsulated.

The pathologist reported two distinct malignancies in the right ovary, a granulosa cell tumor and a papillary cyst-adenoma (Figs. 1 and 3). On microscopic examination no abnormal changes of the left ovary were noted.



Fig. 3.—Section of right ovary, showing granulosa cell tumor invading ovarian stroma.

The patient's postoperative course was uneventful and she was discharged in good condition.

This case is of additional interest, because it represents a granulosa cell tumor of the ovary following irradiation therapy. Since the original description of a typical granulosa cell tumor of the ovary by von Kahliden<sup>7</sup> in 1895, a number of reports have appeared in the literature, so that now approximately three or four hundred cases have been recorded. Difficulty in collecting the reported cases has been encountered because of the diverse terminology employed before 1914, when von Werdt<sup>8</sup> suggested its current appellation, "granulosa cell tumor of the ovary." Attempts to clarify this confusion and to correlate the mass of clinical and histologic information were made by Te Linde<sup>9</sup> in 1930, Bland and Goldstein<sup>10</sup> in 1935, Pratt<sup>11</sup> in 1937, and Schulze<sup>12</sup> in 1939. Based on these series of collected cases, the clinical picture has been definitely established. However, the histogenesis remains a speculative problem, as attested by the numerous current etiologic theories.

We have had only one other patient with a malignancy following radiation therapy, a comparatively young woman with a cystadenoma of the ovary developing two years after intensive radiation for adenocarcinoma of the uterus. Whereas conclusive evidence remains to be offered, the possibility of irradiation as an inciting factor in the development of primary malignant neoplasms is too great to be disregarded. Because of the numerous factors involved and because the histogenesis of malignancies in general is still obscure, it is extremely difficult to establish such a premise.

the digits becoming joined by the reparative processes which follow amputation, in a manner similar to that in which secondary syndactylia may occur after severe burns if precautions are neglected.

It is now clear<sup>1</sup> that congenital amputations are not produced by any of the frequently suggested extrinsic mechanical agencies, such as ligature by amniotic bands or by the umbilical cord. The process operates intrinsically. While lack of vital



Fig. 1.—The infant at about one week.

Fig. 2.—The deep annular cleft of the right upper arm.

Fig. 3.—Right hand. Note wrist drop.

Fig. 4.—Left hand. Note amputation of index and furrows encircling the middle finger.

On April 14 the obstetric department was asked to see the patient. Neither before nor after this date was there any difficulty incident to pregnancy. There was no vaginal bleeding, and all the findings in obstetric examination were entirely normal. X-ray of the pelvis showed slight callus about the fractures, but there was no evidence of pelvic obstruction.

On May 4 the patient was discharged. She returned later for change of cast, and with approach of the date of expected delivery entered the obstetrical ward on July 8. The blood pressure was 120/80; pulse, 80; temperature, 98.4° F. A cast was still present on the right leg, which emitted a foul odor. The pelvic measurements were normal, the presentation was vertex R.O.P., and the fetal heart sounds were 140 in the R.L.Q. There was apparently no disproportion. A final x-ray of the pelvis showed no evidence of obstruction or bone displacement.

Labor began July 10. After a normal course for fifteen hours and 50 minutes a male child, weighing 6½ pounds, was spontaneously delivered. The child cried immediately at birth. The puerperium was uneventful and the mother was discharged eight days later. The infant was held in the hospital, where it has remained until the present time (January, 1941), for observation and treatment.

The infant presented multiple congenital amputations as characterized below, but otherwise there were no externally evident abnormalities. There were no abnormalities evident in the mother nor, according to her statement, in other members of the family.

1. The most conspicuous defects involved the right arm (Fig. 1). There was a deep cleft completely encircling the upper arm slightly above its middle (Figs. 1 and 2). The musculature of the lower arm and hand was atrophic (or hypotrophic?). The transverse dimensions of the lower arm and hand were smaller than on the left side, and there was a pronounced wrist drop (Figs. 1 to 3). All bones of the right arm and hand were less robustly formed than those of the left. The lower arm and hand were pallid and cold.

2. The left hand (Fig. 4) showed a completed amputation of the middle and terminal segments of the index finger and amputation of the terminal segment of the ring finger. There were several encircling and irregularly disposed clefts on the middle finger. Depending freely from the end of the index, there was a thin catgut-like strand, and there were several similar threads uniting the index and middle fingers.

3. On the right foot the distal segments of the first three digits were amputated, and their stumps were syndactylous.

A plastic operation was performed on the right arm with the aim of relieving compression at the level of the annular cleft. This was followed by improved circulation in the lower arm and hand, but the wrist drop has persisted. Except for a pneumonia, the infant has been in good health, and is now (January, 1941) about to be discharged.\*

The infant conforms to the typical picture of congenital amputations (Streeter<sup>1</sup>) with respect to the occurrence of multiple amputations and furrows, though it is unusual in presenting involvement at a level above the elbow. Portions of some digits are actually amputated, while the annular furrows of the right arm and of the middle finger of the left hand represent the same principle of affection, differently localized and expressed. The history of fetal amputations has been traced by Streeter<sup>1</sup> and the mechanism has been further discussed by Cummins<sup>2</sup> and Keith.<sup>3</sup> In Streeter's earliest specimen, of fourteen weeks' menstrual age, the process is already well advanced. When there is actual amputation, it is brought about by necrosis and sloughing, with occasional remains persisting in the form of strands, such as are observed in the left hand of the present case. The characteristic annular furrows are considered to result from local deficiency in the growth capacity of the tissues, of less severe grade than that leading to sloughing. Not uncommonly, as in the right foot of this case, there is coexistent amputation of digits and syndactylia of their remaining stumps. Coleman,<sup>4</sup> and others have raised the query as to whether there may be a causal relationship between these concurrent abnormalities. Our own conclusion is that the syndactylia is secondary to amputation,

## PREGNANCY COMPLICATED BY SEVERE GASTRIC HEMORRHAGE

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THE following case is being reported because of the rare occurrence of severe gastric hemorrhage occurring in a pregnant woman at term. Only two reports could be found in the literature on similar types of cases, and no mention of the subject could be found in any of the standard textbooks on obstetrics.

Sturrock,<sup>1</sup> in 1913, reported a case of gastric hemorrhage occurring at the time of delivery, but this case was in no way comparable to the one we are reporting. Subsequent studies were not done and no adequate explanation was given for its cause.

Preiss,<sup>2</sup> in 1907, reported the case of a woman who had a similar accident in her second and third pregnancies. Her first pregnancy was entirely normal. The second pregnancy, fifteen months later, and the third, three years after the second, were complicated by the occurrence of sudden severe gastrointestinal hemorrhages evidenced by vomiting of blood, passage of bloody stools, and shock. In both pregnancies, the bleeding occurred about two weeks before the expected date of confinement and was not associated with any previous gastrointestinal symptoms. In both instances, the onset of labor and delivery were spontaneous within twenty-four hours after the bleeding. The birth of normal, deadborn, male infants was the result in both pregnancies; the fetal hearts were lost during labor without any apparent cause. The puerperiums were normal in both pregnancies, and in the second pregnancy no special diet was given. The author discusses the possible causes of the bleeding and comes to the conclusion that it was due to a ruptured gastric varix produced by the mechanical stimulation of solid food.

Contrary to our experience, both Sturrock and Preiss make the statement that gastrointestinal hemorrhage during pregnancy is not an uncommon complication. In going over the records of the New York Hospital and the Berwind Maternity Clinic, no such complication occurred during labor in 27,942 deliveries. There was, however, one case of moderately severe hematemesis in a five months pregnant woman, who improved on bed rest and diet and went to term without further complications.

Our patient was a 31-year-old gravida ii, para i, who was admitted to the obstetrical service on Feb. 6, 1940, approximately one week before her expected date of confinement, because of vomiting of blood and passage of tarry stools for twenty-four hours. The first pregnancy had been uncomplicated and resulted in the spontaneous term delivery of a normal female infant, 3,220 gm., three years prior to the present pregnancy. The patient stated that during the latter months of her pregnancy she had vague attacks of indigestion, which she described as "heartburn," and that these often occurred during the night, following the ingestion of food before retiring. However, this symptom had been present during her first pregnancy and was similar to the complaints of a large percentage of pregnant women. For several days prior to admission she had had occasional dizzy spells and was easily fatigued. The pregnancy had otherwise been uncomplicated. The Wassermann test was negative. The weight gain was 20 pounds (from 114 to 134 pounds), and the blood pressure ranged between 110 and 120 systolic over 70 to 80 diastolic. The urine on all occasions was free from albumin and sugar.

There had been no previous hematemesis or tarry stools. She gave a history of having had some gastrointestinal complaints in 1935. A gastrointestinal series, done at that time, showed a ptosis of the stomach and colon.

capacity of the tissues is demonstrated in the observed pathology of fetal amputations, a fully satisfactory explanation of its etiology is not yet available. From observations upon what is evidently the same condition in animals it appears that amputative processes arise primarily as a result of germinal defectiveness. Bagg and Little,<sup>5</sup> and Bagg<sup>6</sup> have produced in the descendants of x-rayed mice a large frequency of congenital defects, including clubfoot, polydactylism, and loss of distal portions of extremities. The x-ray exposure so alters the reproductive cells that embryos which they produce are thus defective. In rats without experimental treatment (Wooley and Cole<sup>7</sup>), the tail, toes, or rarely an entire foot may be involved in amputations, occurring usually between ten and twenty days after birth. This process in the rat has a germinal basis, and a probably recessive heredity. The deficiency may be regarded as due to a "susceptibility factor," for which the animal will suffer if other influences make it manifest. Again in the rat, a mild amputative tendency evident as slight annular constrictions is reported by McElroy and Goss,<sup>8</sup> arising in animals maintained on diets deficient in vitamin B<sub>6</sub>; its appearance in only 10 per cent of the animals restricted to the same depletion diet is suggestive of a susceptibility factor.

From consideration of other reported instances of congenital amputations in human subjects\* and of the parallel conditions observed in mice and rats, we conclude that the amputations in the present case are to be explained as the result of incapacity which was inherent in the developing embryo. But since actual manifestation of that incapacity might have been dependent upon the coexistence of other influences, the possible roles of known incidents of the prenatal history should be examined. The maternal injury in early pregnancy might be suggested as a possible source of developmental disadvantage. If it were a factor, the injury presumably would have operated mechanically, by disadjustment of the fetal-maternal circulatory relationships. There is the further possibility of vitiation of the fetal environment by toxic substances and fever incident to osteomyelitis. The brief x-ray exposures to which the fetus was subjected in making plates of the pelvis may be definitely ruled out as a causative agency. Neither of the two suggested possible factors can be absolutely excluded, though it would be difficult to substantiate their influence. On the other hand, there are two indications against etiologic significance of the maternal injury and its consequences. The more cogent is the conclusion of Streeter,<sup>1</sup> with which Keith<sup>3</sup> as well as the present authors agree, that the onset of amputative pathology is at a considerably earlier period than that of the maternal accident in this case. Second, congenital amputations occur in infants delivered by women having no history of trauma or infection, showing that such circumstances are not requisite for production of the defect.

#### REFERENCES

- (1) *Streeter, G. L.*: Contrib. to Embryol., Carnegie Inst. of Wash. 22: 1, 1930.
- (2) *Cummins, H.*: Breunemann's Practice of Pediatrics 4: Chap. 24, 1937.
- (3) *Keith, Arthur*: Brit. J. Surg. 28: 173, 1940.
- (4) *Coleman, H. A.*: J. A. M. A. 83: 1164, 1924.
- (5) *Bagg, H. J., and Little, C. C.*: Am. J. Anat. 33: 119, 1924.
- (6) *Bagg, H. J.*: Am. J. Anat. 43: 167, 1929.
- (7) *Wooley, G. W., and Cole, L. J.*: J. Heredity 29: 123, 1938.
- (8) *McElroy, L. W., and Goss, H.*: Proc. Soc. Exper. Biol. & Med. 45: 717, 1940.

\*The limits of a case report do not admit a full listing of the literature consulted, but we wish to direct attention to an important early monograph on congenital amputations which has escaped the attention of recent writers on the subject: Montgomery, W. F.: An Exposition of the Signs and Symptoms of Pregnancy: with some other papers on subjects connected with midwifery. From the second London edition, 1857. Philadelphia, Blanchard and Lea.

presence of an ulcer or eroded area. Hematemesis may be associated with a variety of conditions, and it may be very difficult or even impossible to demonstrate the etiologic factor.

We are at a loss to explain any cause for the intrauterine death of the fetus and the tetanic state of the uterus during labor. Strangely enough, the case reported by Preiss produced the same result. We might postulate, tentatively, that severe gastrointestinal bleeding might affect the uterine circulation sufficiently to produce the syndrome characterized by death of the fetus and tetanic contraction of the uterus. Yet the same result is not associated with hemorrhage from placenta previa.

#### REFERENCES

- (1) *Sturrock, W. D.*: Brit. M. J. 1: 218, 1913. (2) *Preiss, E.*: Gynack, Rundschau 1: 725, 1907. (3) *Balfour, D. C.*: Collected Papers, Mayo Clinic 14: 53, 1922. (4) *Eusterman, G. B.*: St. Paul M. J. 15: 587, 1913. (5) *Balfour, D. C.*: J. A. M. A. 73: 571, 1919. (6) *White, W. H.*: Lancet 2: 1189, 1906.

## WATERS CESAREAN SECTION IN A PATIENT WITH GAS BACILLUS AND MIXED INFECTION

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THE Waters section for infected patients may be an outstanding contribution to obstetric surgery. The original communication<sup>1</sup> establishes its anatomic superiority over similar operations and, with a series of 60 cases without maternal death, suggests technical safety. But its behavior in the clinical test of actual infection still is unproven: only 1 of Waters' 60 patients is recorded as infected, although 14 had preoperative fever. And we have found no other papers on the operation. Nowadays infections serious enough to offer it a stringent test are unusual.

#### CASE REPORT

A 32-year-old primipara (Clinic No. 14711) had dependent edema (Grade 2), albuminuria (Grade 4), evidences of severe pyelonephritis, and blood pressure of 155/82 with, incidentally, a history of systolic pressure over 200 for some weeks before. We saw her first after seventy-two hours of satisfactory labor pains, when, despite the absence of bony disproportion and with no history of cervical disease or operation, the cervix still was only one finger dilated. Several vaginal examinations and attempts at manual and instrumental dilatation had been made since rupture of the membranes, which had preceded by eight hours the onset of pains. There was a thin, foul vaginal discharge. The temperature was 100.2° F., the weak pulse 120 and the leucocyte count 20,500.

After four hours' rest by morphine, during which sulfanilamide and parenteral fluids were begun, a Waters section under spinal anesthesia and a transfusion were done. It was recorded that opening the uterus released "a stench like that of appendiceal peritonitis, not at operation but at autopsy." The baby died the next day, and post-mortem examination showed general sepsis of two or three days' estimated duration. The mother's convalescence was stormy, with uremia, serum sickness, metastatic infections, and septicemia. Despite a large subperitoneal abscess, evacuated by rectum on the thirteenth day, there was no evidence of peritonitis, and she was discharged relieved on the thirty-sixth day. The organisms recovered from the uterine cavity were hemolytic staphylococci and streptococci, various bacilli, and *Clostridium welchii*.

The chief postoperative treatments were double-time Elliott therapy, sulfanilamide, and, for the gas bacillus, roentgen therapy and antitoxin.

On admission at 4:00 P.M., the patient was rather pale but in good condition. The pulse was rapid but of good quality. The examination of the chest was essentially negative, the heart was not enlarged, rhythm regular, and blood pressure 125/85. She complained of nausea on palpation of the abdomen.

The red blood count was 3,020,000; hemoglobin 72 per cent Sahli. The urine showed no albumin or sugar, and the microscopic examination was negative.

At 6:15 P.M. she vomited 700 c.c. of partially clotted blood and complained of faintness and dizziness. The blood pressure fell to 96/50; pulse was 130 and of fair quality. Rectal examination revealed tarry stool on the examining finger. She was given 0.015 gm. of morphine sulphate every four hours by hypodermic injections with nothing by mouth. In addition to this, she was given a transfusion of 400 c.c. of citrated blood. Ice bags were applied to the upper abdomen. At 8:00 P.M. she vomited 300 c.c. more of older-appearing blood clots, but there was no appreciable change in her condition at this time.

The following morning the patient seemed more comfortable; the pulse was of good quality but was still rapid, 130 per minute; blood pressure 94/60; the hemoglobin was 62 per cent. No additional vomiting occurred. She was given another transfusion of 350 c.c. of citrated blood.

The fetal heart was not heard after 6 A.M., and fetal movements were not felt after this time. Labor started spontaneously at 9:00 A.M. The membranes ruptured at 9:05 A.M. The contractions at this time were mild, coming every seven to ten minutes apart. At 12 NOON the uterus was noted to be tetanically contracted but not tender; only the lower uterine segment relaxed between pains. At this time we thought that we were dealing with a premature separation of the placenta. The cervix at this time was effaced and 2 to 3 cm. dilated, with the head at the spines in an L. O. A. position.

Labor progressed rapidly and at 2 P.M. the patient was delivered by low forceps under light gas oxygen anesthesia. The baby was a deadborn, not macerated, male infant, weighing 2,530 gm. The placenta separated three minutes later and was expressed from the vagina by Schultze's mechanism. Gross and microscopic examination of the placenta revealed no evidence of premature separation or any other abnormality. The total blood loss was estimated at 50 c.c. Five hundred cubic centimeters of 5 per cent glucose were given following delivery, and the patient was returned to her bed in good condition.

At 9:00 P.M. another 500 c.c. of glucose were given. The patient was placed on a Sippy regime along with vitamin K by injection and vitamin C by mouth. Infusions of 500 c.c. of 5 per cent glucose were given on the first two post-partum days. There was no further hematemesis and the stools were negative for occult blood. Four cubic centimeters of iron ammonium citrate (50 per cent solution) were given three times a day.

On February 28, a gastrointestinal series revealed visceroptosis with no evidence of peptic ulcer or other pathology. Her diet was gradually increased, and she improved rapidly under conservative treatment and the administration of vitamins B and C. At the time of her discharge, four weeks following delivery, she was very much improved and feeling well. At this time her hemoglobin was 80 per cent and her red blood count 4,360,000.

Six weeks following discharge, the patient had no suggestive symptoms and had gained 5 pounds in weight. The blood pressure was 126/70, hemoglobin 96 per cent, and red blood count 4,790,000. Physical examination was essentially negative. Since that time, the patient has been perfectly well.

#### DISCUSSION

On admission to the hospital it was felt that the patient had either a bleeding peptic ulcer or a ruptured varix. In view of the negative gastrointestinal series, the patient, in all probability, had a severe gastritis with subsequent erosion of a blood vessel. Not infrequently do we see individuals who have a severe hemorrhage with subsequent x-ray examinations failing to reveal any defects. Hemorrhage is merely an incident and may bear little relation to the size, the site, or even the



The latter proved to be a tubular adenocarcinoma. Following several courses of roentgen therapy to the operative site, the patient remained perfectly well until the initiation of pregnancy in the fall of 1939. Her last menstrual period had occurred on Sept. 7, 1939, and the patient required hospitalization on Dec. 7, 1939, because of hyperemesis gravidarum associated with severe tachycardia and marked weight loss. The basal metabolic rate was found to be plus 64 per cent. Medical treatment for hyperthyroidism was instituted and, on Dec. 29, 1939, with the basal metabolic rate reduced to plus 32 per cent, subtotal thyroidectomy was performed. The patient's convalescence was uneventful, the state of gestation remained undisturbed, and she was discharged from the hospital on Jan. 21, 1940, with a basal metabolic rate of plus 14 per cent. A few days later, on Jan. 24, 1940, the patient reported quickening. In the middle of February, she first observed several petechiae on both arms and, shortly thereafter, experienced bleeding from the gums and epistaxis. Hospitalization was occasioned two weeks later because of increased mucosal bleeding and the appearance of painful uterine contractions.

On admission to the hospital, the patient was afebrile, had a blood pressure of 122/76 and presented no signs of toxemia. There was moderate bleeding from the gums and from both sides of the nasal septum. The uterus, palpable to just above the navel, contracted vigorously at irregular intervals. Fetal motion was apparent, but fetal heart tones were not audible. On rectal examination, the cervix seemed to be effaced and undilated. Laboratory studies at this time revealed the presence of a hypochromic anemia, with the level of hemoglobin at 70 per cent (Sahli), and a platelet count of 140,000. Coagulation, bleeding, and clot retraction times, the prothrombin determination and a Wassermann reaction were all normal. The medical consultant suggested the diagnosis of "symptomatic purpura, possibly related to the recent hyperthyroidism." The daily treatment included the intramuscular injection of 2 mg. of progesterone and the intravenous administration of 100 mg. of cevitamic acid in 250 c.c. of matched whole blood. The uterine contractions abated and the patient seemed to improve.

At 4 A.M., March 18, 1940, five days after her admission, the patient was awakened from sleep by the initiation of premature labor which terminated six hours later with the spontaneous delivery of female triplets. Each of the first two infants was stillborn, macerated, measured 32 cm. in crown-heel length and weighed less than 700 Gm. The third baby, weighing 706 Gm. and measuring 33 cm. in crown-heel length, was feebly alive at birth but died three hours later. The placenta and membranes delivered spontaneously ten minutes after the birth of the last child. The patient suffered no laceration but bled profusely (more than 800 c.c.) from the uterus which failed to contract, despite the use of obstetric pituitrin, ergonovine, and a firm intrauterine pack of 5 yards of two-inch gauze. The patient continued to bleed through the packing, and the uterus was repacked after thirty minutes. She was given 1,000 c.c. of 10 per cent solution of glucose intravenously and, shortly thereafter, 500 c.c. of matched whole blood. Post-partum treatment included the oral administration of ergonovine, the hypodermic use of moccasin snake venom, and a daily blood transfusion. The epistaxis ceased and the bleeding from the gums diminished.

Forty-eight hours after her delivery, the patient began to bleed through the previously undisturbed uterine packing. The uterus was repacked with three-inch iodoform gauze and the same therapeutic regimen continued. The bleeding from the mucosal surfaces ceased and the uterine packing remained dry. The latter was removed after seventy-two hours, on the fifth post-partum day. No further hemorrhage occurred. The patient was febrile while the packing was in place but remained free from temperature after the seventh post-partum day. At the time of the patient's discharge from the hospital, on April 3, 1940, the fifteenth post-partum day, the uterus was well involuted, the hemoglobin value was 76 per cent (Sahli) and the platelet count was 200,000. The patient, maintaining her weight and menstruating normally, has remained well to date (January, 1941).

*Pathologic Report.*—The triple cord placenta, 18 cm. in diameter, was studded throughout with areas of focal hemorrhage which were especially prominent about

## COMMENT

Here was a patient, already a doubtful risk from toxemia and pyelonephritis, with cervical dystocia and established virulent infection by the gas bacillus\* and other organisms following a long dry labor. A Waters section was done. The child died but the mother lived.

The method of operation apparently kept walled-off from the peritoneal cavity, and within the range of chemo-, sero-, heat and roentgen therapy, a large sub-peritoneal abscess.

Waters' operation is extraperitoneal from start to finish and gives exposure that is really surgical. Its relative simplicity is no small argument for a technique which, fortunately, few of us often will need to use. The case reported here suggested two further simplifications:

Technically, the crux of the operation is the separation from the bladder of the deepest layer of perivesical fascia, the layer directly on the vesical veins. Along the midline, especially anteriorly at the urachus, this fascia is fused tightly to the bladder. Also, the guiding veins are fewer in the midline. Start the dissection, then, as in cystectomy: not right across the dome, but separately on each side of the midline, and continue separate dissections all the way down to the uterus itself. At this depth the midline fusion has ceased, and a finger can pass from side to side. On this finger as a guide, cut the tensed median line of fusion by sharp dissection.

Finally, we would suggest draining via the anterior vaginal vault rather than uphill through the incision.

## REFERENCES

- (1) *Waters, E. G.*: AM. J. OBST. & GYNEC. 39: 423, 1940. (2) *Cosgrove, S. A., and Barry, T. A.*: New England J. Med. 222: 344, 1940.

## PURPURA HEMORRHAGICA COMPLICATING PREGNANCY

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PURPURA hemorrhagica is an uncommon complication of pregnancy, there being approximately 75 instances reported to date. Purpura may appear during pregnancy in its primary or idiopathic form<sup>1</sup> and also as a secondary or symptomatic manifestation of either latent toxemia<sup>2</sup> or drug allergy.<sup>3</sup> Multiparas are more often affected than primigravidas, and the dyscrasia tends to occur in the latter half of pregnancy.<sup>1</sup> It is, in any case, a serious complication, with a mortality of more than 55 per cent.<sup>4</sup>

The case history herein recorded is of unusual interest because the patient, having previously had a nephrectomy for carcinoma, underwent a subtotal thyroidectomy because of hyperthyroidism in the first trimester of pregnancy, developed purpura hemorrhagica during the second trimester, prematurely delivered previable triplets, suffered several severe post-partum hemorrhages, and recovered.

## CASE REPORT

Mrs. E. S. (Mount Sinai Hospital No. A 18863), white, twenty-one years of age, was admitted to the hospital on March 13, 1940, because of threatened premature labor at six months of pregnancy in association with bleeding from the gums and epistaxis.

The patient first came under observation in 1935 when, at the age of sixteen, her left kidney was removed because of hematuria and the presence of a palpable tumor.

\*For a discussion of the role of *Cl. welchii* in intra-partum infection, see Cosgrove and Barry.<sup>2</sup>

The weekly dosage of neoarsphenamine was 0.45 Gm. In the mapharsen series there was some variation in the dosage. The first patients treated with mapharsen received 0.03 Gm. at each injection. Finding that the drug was well tolerated and believing this amount inadequate, we changed the dosage six weeks later to 0.04 Gm. Ten months later we again increased the dosage of mapharsen, and we are now giving 0.05 Gm. Since this study covers the period from Sept. 1, 1938, to March 1, 1940, the majority of the mapharsen patients received the 0.05 Gm. dose. None of the patients included in the study received all 10 treatments of mapharsen in the 0.03 Gm. dosage.

TABLE I. COMPARISON OF FETAL MORTALITY AND SEROLOGY IN MOTHER

	TOTAL NUMBER OF MOTHERS	FULL TERM ALIVE		PREMATURE ALIVE		BORN DEAD OR DIED		NEGATIVE LABOR SEROLOGY	
		NUM-BER	PER CENT	NUM-BER	PER CENT	NUM-BER	PER CENT	NUM-BER	PER CENT
Mapharsen	155	125	80.64	24	15.48	8	3.88	65	41.93
Neoarsphenamine	116	101	87.07	10	8.62	6	4.31	45	38.79

## RESULTS

One hundred and fifty-five patients treated with mapharsen and 116 patients treated with neoarsphenamine are included in this study (Table 1). In the mapharsen series, there were 80.64 per cent full-term live babies, 15.48 per cent premature alive, with 3.88 per cent born dead or dying in the hospital. In the neoarsphenamine series comparable figures are obtained: 87.07 per cent full-term live babies, 8.62 per cent premature alive and 4.31 per cent born dead or dying in the hospital. In the mapharsen series, 41.93 per cent and in the neoarsphenamine series 38.79 per cent showed negative blood tests.

There were two sets of twins in the mapharsen series and one set in the neoarsphenamine series.

TABLE II. COMPARATIVE FOLLOW-UP STUDIES OF LIVE BABIES

	TOTAL NUMBER OF LIVE BABIES	BABIES RECEIVING FOLLOW-UP EXAMINATIONS		TOTAL NUMBER PROVED SYPHILITIC	PER CENT TOTAL PROVED SYPHILITIC	PER CENT FOLLOW-UP PROVED SYPHILITIC
		NUM-BER	PER CENT			
Mapharsen	147	84	57.14	6	4.08	7.14
Neoarsphenamine	110	64	58.18	5	5.54	7.81

Table II presents a comparison of the follow-up study on the live babies delivered in the two series. The follow-up study included a Wassermann or Kahn or both on all the babies reported upon, with a complete physical examination in the majority. Eighty-four babies were examined in the mapharsen series, or 57.14 per cent of the live babies in this series. This latter figure is comparable to the one obtained in the neoarsphenamine series, i.e., 64 reports, or 58.18 per cent. In the mapharsen series, 6 babies, or 4.08 per cent, were proved to be syphilitic; in the neoarsphenamine series, 5, or 4.54 per cent, of the babies were proved to be syphilitic. Figuring the percentage of babies with proved syphilis on the basis of the number of reports obtained, we again arrive at comparable figures: in the mapharsen series 7.14 per cent and in the neoarsphenamine series 7.81 per cent of the babies were syphilitic.

Table III is a detailed analysis of the babies that were born dead or that died in the hospital. All had x-ray studies of the long bones. All these x-ray films were read by one person. Only two of the dead babies had any of the signs of congenital syphilis. Both of these weighed less than 1,500 Gm.; both were in the

the umbilical veins. The post-mortem examination of the triplets revealed no gross abnormalities, but multiple areas of cerebral hemorrhage were noted in each by histologic examination.

#### SUMMARY

The history of a 21-year-old primigravida, salvaged from adenocarcinoma of the kidney, is presented because she survived hyperthyroidism and purpura hemorrhagica during pregnancy. The former responded to subtotal thyroidectomy; the latter resulted in premature labor and severe post-partum hemorrhage. Two of the previable triplets, prematurely delivered three months prior to term, were stillborn, and the third died several hours after birth.

#### REFERENCES

- (1) *Rushmore, S.*: AM. J. OBST. & GYN. 10: 553, 1925. (2) *Liebling, P.*: Ibid. 11: 847, 1926. *Siegler, S. L.*: Med. Rec. 139: 189, 1934. (3) *Peshkin, M. M., and Miller, J. A.*: J. A. M. A. 102: 1737, 1934. (4) *DeSaussure, H. W., and Townsend, E. W.*: AM. J. OBST. & GYN. 29: 597, 1935.

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## TREATMENT OF SYPHILIS IN PREGNANCY

### A COMPARISON OF ARSENICALS

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(From the Department of Obstetrics and Gynecology, Emory University School of Medicine)

IN SEPTEMBER, 1938, at the Colored Division of Grady Hospital, Atlanta, it was decided to compare the use of mapharsen, the hemialcoholate of parahydroxyphenylarsine oxide hydrochloride, with that of nearsphenamine in the prevention of congenital syphilis.

The patients studied were all negroes. The only criteria used in the two series were that each prospective mother should have a positive Wassermann or Kahn test before treatment was started and that each patient studied should have received at least 10 treatments with either mapharsen or nearsphenamine at weekly intervals during the course of her pregnancy. In the vast majority of the patients both Wassermann and Kahn tests were positive.

#### METHOD

We specified at least 10 treatments so that we could form a comparison of the value of the two drugs. Our experience has taught us that this number of treatments will, as a rule, prevent congenital syphilis. To give only 10 treatments with one of the arsenicals, however, is not the routine of our clinic. We give weekly injections of one of the arsenicals from the time the patient presents herself until the termination of pregnancy unless some contraindication arises. Consequently, many of the patients included in both the mapharsen and nearsphenamine series received as many as 27 weekly treatments of one drug or the other.

The conditions under which the two drugs were given were the same, with one exception. All patients attended the same morning clinic and all received the same antenatal instructions regarding diet, care of the bowels, etc. Distilled water was used as the diluent in both series. The one exception was that 25 c.c. of distilled water was used to dilute the dose of nearsphenamine and only 10 c.c. was used with mapharsen.

# SULFONAMIDE SUPPOSITORY IN THE TREATMENT OF ACUTE GONORRHEA IN WOMEN

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*(From the Department of Gynecology, Medical College of Virginia)*

IT IS well known that ambulatory treatment of acute gonorrhea has always been attended by a large incidence of complications, including Bartholin abscess, chronic Skenitis, salpingitis, and endocervicitis. Nevertheless, economic considerations still demand ambulatory treatment in many patients, and this study was made on such a group.

The last two years have seen many publications describing the treatment of acute gonorrhea by the oral administration of sulfonamide. It is interesting to note that the urologist has been more enthusiastic about his clinical results than has the gynecologist. This may be due to the chemotherapeutic effect of the drug passing over the male urethra after being excreted by the kidney.

In this out-patient service, 25 cases of acute gonorrhea were observed and proved by history, laboratory, and pelvic examination. These patients were treated by the oral administration of sulfonamide, 80 gr. daily for the first three days, and 60 gr. thereafter for two weeks. Bi-weekly examinations of the blood and urethral and cervical smears were taken. In this group, treated as described, without any local therapy, one patient had a negative smear at the end of one week; 3 patients had negative smears at the end of two weeks. The other 21 patients had clinical and laboratory evidence of gonorrhea when the seventeen-day course of therapy was completed. Eighteen of the 25 cases could be followed for three months. During this period 3 of them developed a Bartholin's abscess, 4 developed evidence of salpingitis, 16 had a persistent endocervicitis, and 6 had a subacute Skenitis. It could not be concluded from the results in this series that sulfonamide administered orally, in the absence of other treatment, was a satisfactory means of treating gonorrhea in women.

Two young girls, aged 4 and 9, were seen with acute Neisserian vaginitis. They were treated with 40 and 30 gr. of sulfonamide, respectively, administered for a period of seventeen days. No laboratory or clinical change in the vaginitis could be seen at the end of the treatment.

After being disappointed by the oral administration of the drug, we observed another series of patients with acute gonorrhea, using the drug locally. Insufflation of the powder was first used but promptly discarded because the powder has a tendency to cake in the vaginal vault, and does not come into contact with the urethra and vaginal introitus. The sulfonamide then was incorporated in a boroglyceride base, using 20 gr. of sulfonamide and 10 gr. of lactose in the suppository. Twenty-five patients suffering from acute gonorrhea were treated by the insertion of one sulfonamide suppository high into the vaginal vault three times a day.

These patients were treated for seventeen days, smears from the urethra and cervix being taken biweekly. It was noted that the symptoms of dysuria and purulent leucorrhea disappeared in 12 of the patients on the third day. Smears from the urethra and cervix were negative in all 25 patients at the end of one week. It was possible to follow 21 of the 25 for a period of three months. Nineteen patients were symptom-free without evidence of urethritis, and there were no cases of Bartholinitis. There was not a single case of salpingitis. One patient, at three months, had an acute gonorrhea which could be traced to an intercourse five days previously with a male suffering from a recently acquired urethral discharge. This patient stated that she had been symptom free up until the onset of this reinfection. One patient had a residual endocervicitis. The most remarkable feature of these 19 cases was the absence of any endocervical infection, this being confirmed by the absence of pus cells in the cervical smears.

TABLE III. DETAILED STUDY OF DEAD BABIES

CASE	WEIGHT AT BIRTH GM.	DRUG*	X-RAY REPORT ON BONES	
1	540	Maph.	Positive	10 treatments, 3 of which were 0.03 Gm.
2	1,400	Maph.	Positive	10 treatments, 5 of which were 0.03 Gm.
3	1,100	Maph.	Negative	
4	1,240	Maph.	Negative	
5	2,310	Maph.	Negative	Intrauterine death 20 hr. after proved gross intra-partum infection.
6	1,810	Maph.	Negative	Respiration poor. Impression of atelectasis. Autopsy refused.
7	1,490	Maph.	Negative	Anatomic diagnosis: Prematurity, congenital atelectasis of lungs, acute dilation of the heart.
8	1,310	Maph.	Negative	
9	2,100	Neo.	Negative	Mother had cardiovascular disease. Blood pressure 230/140 during labor. Catheter and bag induction. Prolonged labor. Autopsy refused.
10	1,140	Neo.	Negative	
11	2,460	Neo.	Negative	Spontaneous delivery. Short labor. Clinical diagnosis cerebral hemorrhage. Autopsy refused.
12	2,185	Neo.	Negative	
13	2,630	Neo.	Negative	Intrauterine death probably due to short cord. Autopsy refused.
14	2,410	Neo.	Negative	Anatomic diagnosis: Tentorial tear with massive intracranial hemorrhage. Also congenital atelectasis of lungs.

\*Maph., mapharsen; Neo., neoarsphenamine.

first group of patients that received only 0.03 Gm. of mapharsen per injection. In the first case, there were 5 doses of 0.03 Gm. and in the second, 3 doses. We believe that an inadequate amount of arsenic was used in these cases, and that they are no reflection on the drug.

There were no severe reactions, immediate or delayed, in either series. Local reactions caused by technical accidents were about the same in the two series. The only notable difference in the toxic reactions was that nausea following the administration of mapharsen did not seem to be as frequent or as severe as with neoarsphenamine.

#### SUMMARY AND CONCLUSIONS

1. Best results in the prevention of congenital syphilis are obtained by early and continued treatment with one of the arsenicals throughout the duration of pregnancy.

2. Mapharsen will prevent congenital syphilis as well as neoarsphenamine and in the patients so far studied is better tolerated.

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teeth. These three pieces are combined into one unit and may be attached to the curette after it has been inserted into the uterus, but before the specimen has been scraped from the uterine wall. By gentle or forceful suction on the bulb, the pressure may be modified at will.

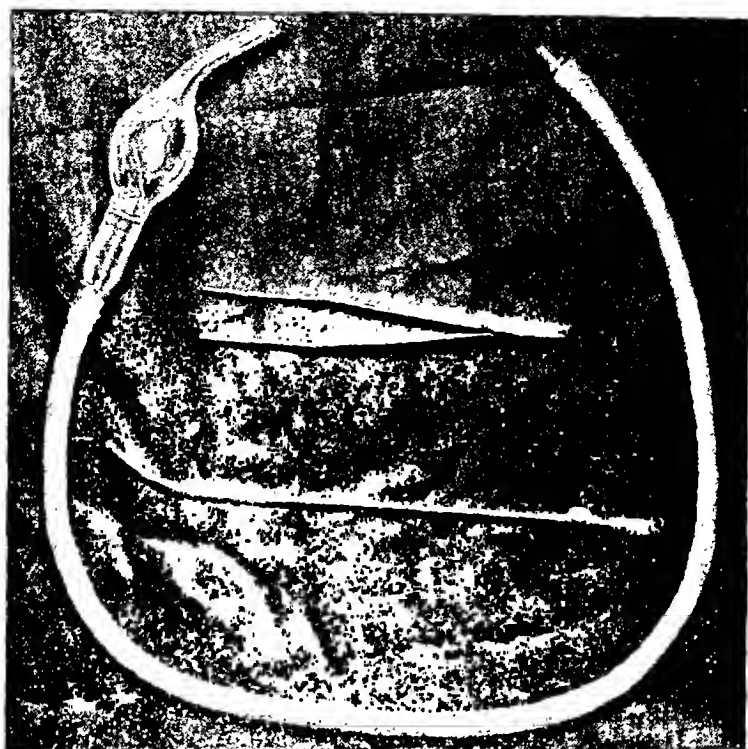


Fig. 1.

In this way, the hands are left completely free for the manipulation of the curette. Two, three, or four specimens may be removed, and easily sucked up into the shank of the instrument. Furthermore, after the curette has been removed from the uterus, the tissue may either be expelled by blowing through the tube, or may be picked out of the curette with a sterile forceps. Thus the curette may be kept sterile, so that if the necessity for removing further specimens arises, it may be reinserted into the uterus without danger of infection.

For office work, it is to be recommended that the entire outfit, including the curette, tubing, bulb, tissue forceps, and gauze be wrapped and autoclaved in a single unit.

#### REFERENCES

- (1) Israel, S. L., and Mazer, C.: *AM. J. OBST. & GYNEC.* 36: 445, 1938.
- (2) Hoffmann, P. E.: *Ibid.* 27: 616, 1934.
- (3) Lorincz, B., and Davis, A.: *Brit. M. J.* 1: 261, 1939.
- (4) Klingler, H. H., and Burch, J. C.: *J. A. M. A.* 99: 559, 1932.
- (5) Novak, E.: *J. A. M. A.* 104: 1497, 1935.
- (6) Randall, L. M.: *Proc. Staff Meet. Mayo Clinic* 11: 58, 1936.
- (7) Kurzrok, R., Wilson, L., and Cassidy, M. A.: *AM. J. OBST. & GYNEC.* 29: 771, 1935.

Two cases of acute vaginitis in children were seen. Local treatment by insertion of sulfonamide suppository resulted in laboratory and clinical cure within the seven-day treatment period.

A careful review of the literature failed to show any report on blood levels of sulfonamide, following the introduction of the drug into the vagina. Twenty-five adult patients treated by the vaginal route were studied at the end of one week, during which time the adult patients had each received 420 gr. of sulfonamide, and the children had each received 280 gr. The blood levels varied from a trace to 4 mg. per 100 c.c. of blood. The higher concentrations were found in children with acute vaginitis. Obviously, the clinical result could not be attributed to the drug which was absorbed. It does demonstrate again that the vaginal mucosa is an absorptive organ, and therefore, care should be exercised in the introduction of new drugs.

### CONCLUSIONS

1. Oral administration of sulfonamide for the treatment of acute gonorrhea in women has little if any value.

2. Sulfonamide locally in the form of boroglyceride suppository probably has real value in the prevention of complications and cure of infection.

3. Sulfonamide is absorbed from the vaginal mucosa in varying degrees, the degree of absorption being more apparent in patients with acute vaginitis.

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## SIMPLIFIED SUCTION FOR OBTAINING ENDOMETRIAL BIOPSIES

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(From the Stuyvesant Polyclinic)

THE value of endometrial biopsy in gynecologic and endocrine diagnosis is obvious, even though Israel and Mazer<sup>1</sup> believe that the removal of small pieces of tissue is of no value, especially in suspected malignancy. Various types of instruments, however, have been devised for the removal of such specimens from the uterus with minimal danger and discomfort to the patient. These include a tiny curette (Hoffmann<sup>2</sup>), an endometrial punch (Lorincz and Davis<sup>3</sup>), and the more commonly used cannula with the closed end and the side opening, the biopsy curette (Klingler and Burch<sup>4</sup>; Novak<sup>5</sup>; Randall<sup>6</sup>). Modifications of the latter instrument have been made by Kurzrok, Wilson and Cassidy.<sup>7</sup> With the punch or biopsy curette, in order that the portion of the endometrium be removed and not lost in the uterine cavity, suction is applied. This pulls the tissue back into the hollow shaft of the instrument, and allows the operator to remove three or four sections without withdrawing the instrument from the uterus.

Suction may be applied either with a glass or metal syringe, equipped with a three-way stopcock (8), or with an electric pump, similar to a breast pump, and connected to the curette by means of a suction bottle and rubber tubing (3). Both of these methods possess disadvantages. The former requires the use of both hands in manipulating the syringe, gives an intermittent type of suction, and possesses an added hazard, in that the operator, forgetting to turn the stopcock before closing the syringe, forces both air and the tissue specimen back into the uterine cavity. The particular disadvantages of the latter method lie in its excessive bulk and unwieldiness, together with its inherent power to ruin the specimen by excessive amounts of suction.

Since the above methods are not satisfactory, the following simple means of applying either negative or positive pressure to the biopsy curette is recommended.

The apparatus consists essentially of a metal Lucr nipple to fit the machined end of the curette, a length of thick-walled rubber tubing, and a DeVries aspirator bulb, the end of which is modified so that it can be held firmly between the lips and



gynecologic practice, since a readily available source of anti-Rh agglutinins for the selection of Rh negative donors is not yet obtainable. Even if an Rh negative donor of the same blood group is on hand, the compatibility test as indicated should not be omitted.

An analysis of the obstetric histories of the women who suffered from hemolytic transfusion reactions because of isoimmunization revealed a high incidence of spontaneous abortions and miscarriages, stillbirths, and neonatal deaths.<sup>2</sup> The clue to this relationship became evident when the bloods of a larger series of women giving such obstetric histories were studied.<sup>4</sup> It was found that these women in many instances showed a striking familial incidence of babies with erythroblastosis fetalis. In the great majority of cases, the bloods of these women were found to be negative for Rh while the bloods of their husbands and their affected infants contained this factor. In a certain proportion of the cases the mother's blood contained anti-Rh agglutinins of varying degrees of intensity.

These findings suggested that erythroblastosis fetalis is the result of (1) isoimmunization of the Rh negative mother by the Rh blood of the fetus and (2) the subsequent passage of mother's agglutinins through the placenta to act on the susceptible blood of the fetus.

*Philip Levine, M.D.*

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**Eschweiler, Paul Chadbourne: Dangers of the Indiscriminate Coverage of Parenterally Administered Glucose With Insulin, Surg., Gynec. & Obst. 71: 141, 1940.**

A usual preoperative or postoperative procedure is to give an infusion of 500 c.c. of 10 per cent glucose "covered" by 25 units of insulin in cases of diabetes mellitus complicated by obstetrical or surgical conditions. Too frequently a hypoglycemic reaction results. A study has been made to determine whether all patients with diabetes mellitus can be expected to tolerate the same amount of insulin with an infusion of glucose. Intravenous glucose tolerance tests were given to 5 patients with diabetes mellitus of various stages of severity and to 1 normal patient. It was determined that insulin is not required to reduce the blood sugar values near to the fasting level after the intravenous administration of 500 c.c. of 10 per cent glucose, as the blood sugars of the patients with diabetes mellitus reached blood sugar levels approximating their usual fasting levels within one and one-half to two hours. It was demonstrated that the milder the case of diabetes the more nearly was approached the curve representing the nondiabetic patient. It may be concluded, therefore, that insulin should never be routinely administered to "cover" parenterally administered glucose in patients with diabetes mellitus. The diabetic status of the patients must be taken into consideration and thus dangerous hypoglycemic reactions may be avoided.

WILLIAM C. HENSKE.

## Editorial

### The Role of Iso-Immunization in Transfusion Accidents in Pregnancy and in Erythroblastosis Fetalis

IN THE course of studying transfusion accidents in pregnancy, observations were made which are of particular interest to the obstetrician and pediatrician.<sup>1-4</sup> These findings paved the way for an improved compatibility test which should considerably diminish the incidence of hemolytic transfusion reactions. Furthermore, the studies revealed data which served as a basis for a theory on the pathogenesis of erythroblastosis fetalis in its various manifestations.

Such transfusion reactions are not due to errors in blood grouping, but are attributable to the presence in the mother's blood of immune intragroup agglutinins. There is evidence that a newly discovered factor<sup>5</sup> in human red blood cells, Rh,<sup>6</sup> if present in the fetus and absent in the mother, can stimulate the mother to produce anti-Rh agglutinins. The Rh factor which is present in 86 per cent of individuals of the white race is inherited as a dominant property, much like the A and B factors of the four blood groups.<sup>6</sup>

It is probable that anti-Rh agglutinins are responsible for about 90 per cent of all intragroup transfusion accidents, after repeated transfusions or in pregnancy at the first transfusion. In short, a certain proportion of Rh negative individuals can produce anti-Rh agglutinins either by immunization with the Rh factor of the fetus or by repeated transfusions with Rh positive donors. This process is referred to as isoimmunization, since the individual producing the antibodies and the individual yielding the immunizing material are in the same species.

In many instances anti-Rh agglutinins react far better at 37° C. than at lower temperature. For this reason the term "warm agglutinin" was applied to them. In this respect they differ from the agglutinins of the grouping sera and other atypical agglutinins. It is, therefore, recommended that in the direct compatibility (cross-matching) the patient's serum and donor's cell suspension be incubated for thirty minutes at 37° C. and then centrifuged at low speed (500 r.p.m.) for one minute.

The modification, i.e., incubation at 37° C. is highly essential for the proper selection of a compatible donor, especially in obstetric and

\*The sera of rabbits prepared by injection of rhesus (Rh) blood and the sera of some pregnant women, serve as reagents to detect this blood factor.

<sup>1</sup>Levine and Stetson: *J. A. M. A.* 113: 126, 1939.

<sup>2</sup>Levine and Katzin: *Proc. Soc. Exper. Biol. & Med.* 43: 343, 1940.

<sup>3</sup>Levine, Katzin, and Burnham: *Proc. Soc. Exper. Biol. & Med.* 45: 346, 1940.

<sup>4</sup>Levine, Katzin, and Burnham: *J. A. M. A.* 116: 825, 1941.

<sup>5</sup>Landsteiner and Wiener: *Proc. Soc. Exper. Biol. & Med.* 43: 223, 1940.

<sup>6</sup>Landsteiner and Wiener: Personal communication.

J. B. Collip, there is a wide divergence between laboratory animal experiments and their application to the human subject, and nowhere is this "species difference" more evident than in the field of sex physiology. It demands collaboration between the clinician and the laboratory which unfortunately is not given sufficient attention. In actual practice the alluring reports emanating from commercial sources often are accepted without restraint and account for failures that may discredit a most valuable remedy. Dr. Hamblen in his presentation is satisfactorily conservative and therefore his book may be commended. It presents the results of careful personal studies in addition to complete summaries of the work of others. An important item is the frank discussion of the various commercial preparations which have become so numerous in recent years that confusion as to their employment is to be expected. Perhaps this portion of the book should have followed rather than preceded the very full description of gynecic physiology and endocrinopathic gynecology. The book is attractively printed and very fully illustrated, although many of the photomicrographs appear inadequate as to size. The bibliographic references at the close of each chapter are ample evidence of the ground covered by the author's reading, as is the subject index. The book constitutes a very valuable addition to American textbook literature.

George W. Kosmak.

Mazer and Israel have written a large monograph on the *Diagnosis and Treatment of Menstrual Disorders and Sterility*.<sup>3</sup> According to them, it is designed as "a guide to the family physician"; to me it appeals as a rich and valuable storehouse of the world's literature covering these subjects, the result of meticulous scanning, careful selection, and correct application.

The symptomatology, the clinical investigations, the office procedures, the explanations of basic principles underlying the various hormonal and other tests are admirably and lucidly described. This praise likewise applies, almost unqualifiedly, to the four introductory chapters which deal largely with the physiologic features of the sex cycle, although I am unwilling to concede that "A late menarche is the signpost of an adolescent endocrine disturbance. . . ." "Attempts, therefore, should be made to correct endocrine deficiency in girls before irreparable damage to the lower genital tract ensues." This dictum requires many qualifications.

The authors, in my opinion, subdivide and catalogue symptoms, such as amenorrhea and uterine bleeding, into exact categories far more rigidly than our present knowledge warrants, and upon this most insecure basis employ and recommend therapeutic measures with an exactitude and selectivity which likewise are entirely unwarranted. The reader will find few conditions for which active therapy is not recommended and still fewer in which, according to the authors, he may not anticipate gratifying results.

The volume concludes with nine chapters dealing with all phases of sterility, including that of the male, habitual abortion, and mechanical and endocrine factors.

R. T. Frank.

This book, *Diseases Affecting the Vulva*,<sup>4</sup> by a well-known British dermatologist deals with dermatologic conditions of the external genitalia. While written ostensibly for the specialist in gynecology, it is so elemental in its approach that it would seem more suitable for the medical student. The first eighth of the volume describes the anatomy and embryology of the organs under discussion. While an attempt is made to present the various clinical conditions as pathologic entities,

<sup>3</sup>*Diagnosis and Treatment of Menstrual Disorders and Sterility.* By Charles Mazer, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, etc., and S. Leon Israel, M.D., F.A.C.S., Instructor in Gynecology and Obstetrics, School of Medicine, University of Pennsylvania. With 108 illustrations, 485 pages. Paul B. Hoeber, Inc., New York City, 1941.

<sup>4</sup>*Diseases Affecting the Vulva.* By Elizabeth Hunt, M.D., Ch.B. (Liverp.), Honorary Physician to the Skin Department, South London Hospital for Women, etc. With 36 illustrations and 18 plates in color. The C. V. Mosby Company, St. Louis, 1940.

# Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

## Review of New Books

### Gynecology

Novak's *Gynecological and Obstetrical Pathology, With Clinical and Endocrine Relations*<sup>1</sup> for the first time assembles and documents the unusually large and long experience of the author in teaching these branches. His effort has been to produce a book which should neither err on the side of too great brevity and superficiality, nor on the other hand, fall into the class of encyclopedic exhaustiveness which would relegate it to a book of reference. This aim has been fulfilled only partially as it will have little appeal to gynecologic pathologists, except in the chapter devoted to the physiologically active ovarian tumors.

The author takes a considerable knowledge of general pathology for granted, wisely, so it appears to me, as unless this basis is already present, neither student nor practitioner would be in a position to evaluate specialistic knowledge. Throughout, the clinical side has been given due weight, with consequent direct applicability of the pathologic findings to clinical medicine. Although the hormonal basis of female genital disturbances is dealt with most briefly, they are described lucidly. This applies particularly to the phenomena of menstruation and the so-called functional diseases of the endometrium. There is an ample and beautifully reproduced collection of microphotographs with proper emphasis on the more common disturbances. A chapter by Dr. Louis M. Hellman on the diseases of the placenta, not including hydatidiform mole and chorionepithelioma, is incorporated. The illustrations of macroscopic conditions are mainly from well-known sources to which due credit has been given and are quite adequate in most instances.

This book will be found of great value to the advanced undergraduate student as well as to the practitioner in studying gynecologic pathology. It will likewise be of utmost use in the study of gynecologic pathology in medical schools where the pathologic material is limited. The short references at the end of each chapter will likewise prove of use in finding the later literature to the appropriate subjects.

R. T. Frank.

With the increasing application of the knowledge of the physiology of the ductless glands to practical problems in the treatment of endocrine disorders, a host of books and articles have been presented in this field. The latter has grown to enormous proportions so that considerable effort is required by the student and practitioner to keep abreast of the advances in the same. Among recent additions is the comprehensive monograph by Hamblen entitled *Endocrine Gynecology*,<sup>2</sup> which is addressed primarily to the practitioner. For that reason, it may be designated as timely and likewise authoritative, because its author has made many contributions to the literature based on personal observations and experiments on endocrinology as applied to gynecology. As stressed in the Foreword by Prof.

<sup>1</sup>*Gynecological and Obstetrical Pathology, With Clinical and Endocrine Relations.* By Emil Novak, Associate in Gynecology, Johns Hopkins Medical School, etc. 496 pages with 427 illustrations. W. B. Saunders Company, Philadelphia, 1940.

<sup>2</sup>*Endocrine Gynecology.* By E. C. Hamblen, B.S., M.D., F.A.C.S., Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine, etc. With a foreword by J. B. Collip, M.D. Charles C Thomas, Springfield, Ill., and Baltimore, Md., 1940.

Dr. Greenhill offers an excellent manual in his *Obstetrics in General Practice*.<sup>8</sup> The book is intended primarily for the general practitioner; the text is clear and concise; and is well illustrated. There is an excellent outline of prenatal care and a discussion of minor ailments during pregnancy. As a matter of fact these two chapters deal with most conditions of which the average pregnant woman complains. Although Greenhill quotes frequently from recent literature, one can feel that many of the practical suggestions offered are those which have been found most useful in his hands.

In his discussion of toxemia of pregnancy, the author presents the new classification proposed by a Sub-Committee on Toxemia of the American Committee on Maternal Welfare. Each group and its major subdivisions are thoroughly explained, so that the differentiation of types of toxemias in the hands of the general practitioner should not be difficult. Although Greenhill has stressed the hormonal cause of eclampsia, according to White, in his consideration of diabetes, he does not make mention of this etiologic factor in the discussion of eclampsia itself. The mechanism of labor and operations occasionally necessary for delivery are well described and illustrated. In an excellent chapter on post-partum care he stresses the need for medical attention during the post-puerperal period. Illustrative tables suggest the dosage of the sulfanilamide compounds in sepsis. There is a short closing chapter on obstetric endocrinology.

This is an excellent book; well arranged; well illustrated; essentially practical; and may be highly recommended to those in general practice.

Philip F. Williams.

The fascinating story of twins and other multiple pregnancies has been presented for lay readers in *Multiple Human Births*<sup>9</sup> by Horatio Hackett Newman, and appears under the aegis of the American Association for the Advancement of Science. The author has made a special study of twins for over twenty-five years and has written a book which should be both interesting and educational not only for the layman but for those with a more scientific background. There are discussed the facts and fictions of twins, types and evaluations, with descriptions of typical and unusual experiences. Special attention is paid to the one-egg Dionne quintuplets. The author describes this remarkable group from a biologic standpoint, and tells many details of their development, education, and personalities. One can regret with the author that the study of the mental and personality differences of the quintuplets, which was carried on for several years, has ceased at the order of their guardians. The author does not regard the "quints" as shining examples of the wonderful effects that environment and training are supposed to produce. Why one-egg twins have an apparent mental telepathy and other similar qualities is explained. On the other hand there is a contrasting record of the life story of one-egg twins who have been reared apart.

This book will answer many questions the general public is fond of asking, will satisfy the amateur biologist, and will allay certain fears harbored by many twins and their parents.

Philip F. Williams.

Since the subject of birth control is as widely accepted today as any other prophylactic measure in medicine, it is well to have such a definite and practical manual as *Techniques of Conception Control*<sup>10</sup> available for physicians and those engaged in public health work. In this small but beautifully illustrated pamphlet, Dickinson and Morris have discussed practically all methods of contraception.

<sup>8</sup>*Obstetrics in General Practice*. By J. P. Greenhill, M.D., Professor of Obstetrics and Gynecology, Loyola University Medical School, Chicago, etc. 448 pages, 112 illustrations. Year Book Publishers, Inc., Chicago, 1940.

<sup>9</sup>*Multiple Human Births*. By Horatio Hackett Newman, Ph.D., Sc.D., Professor of Zoology, University of Chicago. Illustrated, 214 pages. Doubleday, Doran & Co., New York, 1940.

<sup>10</sup>*Techniques of Conception Control*. By Robert Latou Dickinson, M.D., and Woodbridge Edwards Morris, M.D., General Medical Director, Birth Control Federation of America. 50 illustrations, 56 pages. The Williams & Wilkins Company, Baltimore, 1941.

this effort is not consistent. The photomicrographs leave much to be desired, many being poorly reproduced. There are eighteen gross color plates, which are well done. That these, however, have not been selected with reference to the relative importance of the various conditions is evidenced by the fact that eleven of the eighteen illustrate varieties of lichen planus. No effort is made to give any accurate data regarding either the incidence or prognosis of the diseases discussed. This is especially reprehensible in the chapter on neoplasms. Furthermore, such important methods of therapy as the use of chemotherapeutic agents in gonorrhea and of estrogenic substances in vulvovaginitis in children are given only cursory attention.

L. M. Hellman.

The second edition of Robson's *Recent Advances in Sex and Reproductive Physiology*<sup>5</sup> has appeared after an interval of six years. The advances in this comparatively short time have been huge and have necessitated much revision, and yet the author has succeeded in keeping the monograph within small compass (329 pages). The new chapter on standardization and determination of activity of the sex hormones is specially à propos and valuable. No clearer, more concise or juster presentation of the present state of this constantly advancing field of biology and medicine can be found.

R. T. Frank.

The third edition of Maguire's *The Anatomy of the Female Pelvis*<sup>6</sup> for the first time is illustrated by excellent and very simple line drawings, based on dissections of sixteen female pelvises. This monograph is of value because it gives a simple and readable description of all the pelvic structures in the female, corresponding to all well-accepted anatomic details.

R. T. Frank.

### Obstetrics, etc.

Six years ago, Dr. Stander revised the last edition of Prof. Williams' classic textbooks on obstetrics.<sup>7</sup> Advances in this branch of medicine have dictated a complete rewriting, with the result that little of the original text remains unaltered. Old chapters have been re-arranged and several new chapters added: "Diseases and Abnormalities of the New-Born," "Classification of Abnormal and Contracted Pelvis," and "Sudden Death and Maternal Mortality." Numerous sections have been rewritten and brought up to date in accordance with developments recorded in obstetric literature. The author's own views are featured, based on the principles taught and practiced in his hospital and medical school affiliations and experiences.

We are dealing practically with a new work in this important branch of medicine which is a worthy successor to the outstanding earlier editions of a man who is generally regarded as one of the foremost American teachers of obstetrics. Professor Williams' textbook for many years occupied an important place in American medical literature. It is a classic which has retained through the labors of Dr. Stander in this Eighth Edition its accepted place as a guide to both student and practitioner.

George W. Kosmak.

<sup>5</sup>*Recent Advances in Sex and Reproductive Physiology.* By J. M. Robson, Lecturer in Pharmacology, University of Edinburgh. With introduction by Professor F. A. E. Crew, Director of the Institute of Animal Genetics, Edinburgh. Second edition, 329 pages with 62 illustrations. Blakiston Company, Philadelphia, 1940.

<sup>6</sup>*The Anatomy of the Female Pelvis.* By F. A. Maguire, Honorary Lecturer in Anatomy; Honorary Gynaecological Surgeon, Royal Prince Alfred Hospital and Prince Henry Hospital in Sydney. Third edition, 162 pages, Illustrated. Angus and Robertson, Sydney, Australia, 1940.

<sup>7</sup>*Williams' Obstetrics.* A Textbook for the Use of Students and Practitioners. By Henricus J. Stander, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College; Obstetrician and Gynecologist-in-Chief, New York Hospital and Director of the Lying-in Hospital, New York City. Eighth Edition. D. Appleton-Century Company, Inc., New York and London, 1941.

past fifteen years. The expansion of this line of thought has made it necessary for an entire re-writing of the book which may properly be taken to represent the ideas of the American Institute of Family Relations. The book is primarily addressed to men. In a highly practical, common-sense manner many points of the various phases of marriage are discussed. To the physician, sociologist, or minister, who has contacts including young people seeking information either for premarital education or solution of the problems of marriage, this book is a source of information of the highest quality. It is so written that it may be handed safely to any man, or indeed to any woman, who is contemplating marriage.

*Philip F. Williams.*

Dr. Corner talks to girls about sex in this small book *Attaining Womanhood*<sup>14</sup> in clear, understandable and easy language. He has described without any sensationalism the reproductive cycle in animals and human beings, and the development of the girl's body before maturity, explaining her physical and mental changes as she passes through the adolescent period. He then describes and discusses sex life in a frank and simple manner and closes the book with a short discussion of the venereal diseases. In this day when so many abnormal aspects of sex life are depicted or suggested by screen and press, it might be well for this book to be read by girls even a little younger than the group for which Dr. Corner intended it.

*Philip F. Williams.*

### Fetus; Newborn; Child

The scattered and often inaccessible data on the physiology of the fetus are well summarized in this small volume, *Physiology of the Fetus*,<sup>15</sup> of 249 pages. Among the more notable of the fifteen chapters are those on fetal blood, fetal circulation, fetal respiration, the genesis and function of the nervous system, and fetal endocrine glands. At the end of each chapter is a list of important references, mostly of recent date. The data presented are derived not only from observations on human and animal material, but also from the experimental results of many current investigators, among whom the author has played a leading role. Particularly stimulating is the presentation of controversial material, such as the discussion of fetal respiration. The evidence on both sides is well presented, and the author's conclusions logically drawn. In addition, suggestions are made regarding the possible course of future investigations. The book is not only an addition to the armamentarium of the embryologist, but should fill a great need for those specialists interested in the newborn infant and in the early neonatal period.

*L. M. Hellman.*

The collaboration of 34 authors with Drs. Holt and McIntosh in writing the eleventh edition of this classic textbook, *Holt's Diseases of Infancy and Childhood*,<sup>16</sup> is an innovation which permits an authoritative revision of the entire work. A successful attempt has been made to avoid the variegated style of the usual multiple-author textbook by the intimate collaboration of the specialists with the present editors in the revision of each section.

The new edition is 181 pages longer than its immediate predecessor. New topics discussed include, among others, cystic fibrosis of the pancreas, inclusion blenorria, petrositis, and regional enteritis. Particularly noteworthy is the increased length

<sup>14</sup>*Attaining Womanhood.* By George W. Corner, M.D., Professor of Anatomy, University of Rochester School of Medicine. 95 pages, illustrated. Harper & Brothers, New York, 1940.

<sup>15</sup>*Physiology of the Fetus.* By William Frederick Windle, Professor of Microscopic Anatomy, Northwestern University Medical School. 249 pages, illustrated. W. B. Saunders Company, Philadelphia, 1940.

<sup>16</sup>*Holt's Diseases of Infancy and Childhood.* By the late L. Emmett Holt and John Howland. Revised by L. Emmett Holt, Jr., M.D., Associate Professor of Pediatrics, Johns Hopkins University, etc. and Rustin McIntosh, M.D., Carpenter Professor of Pediatrics, Columbia University, New York, etc. Eleventh edition, 262 figures, 1,421 pages. D. Appleton-Century Company, New York, 1940.

The application of these various methods is clearly described and illustrated and should assist in the adequate instruction of married couples in the proper desire to space children. The authors regard the control of conception of equal importance in medicine with the control of infection, pain, and communicable diseases.

This type of presentation of the subject will do much to advance the control of conception to its proper place in the community.

*Philip F. Williams.*

Since contraception is becoming an integral part of every maternal health program such a report as this *Controlled Fertility: An Evaluation of Clinic Service*<sup>11</sup> by Regine K. Stix and Frank W. Notestein is important. The authors have attempted to show the effects of contraceptive practices on fertility, to evaluate the influence of the clinic services, and to consider the place of such a clinic as an agency of public health and welfare. The patients of the Birth Control Research Bureau in New York have been used in this group study. Some question arises as to whether or not this group was a conditioned one, as 96 per cent of them had practiced some form of contraception before they attended this clinic. A new statistical approach is made to the problem by using pregnancy rates instead of case failure ratios.

Some interesting statements are noted in regard to the difference in birth rates in three religious groups. Of the pregnancies occurring in these clinic patients, less than 70 per cent ended in live births, while more than 20 per cent were terminated by illegal abortion. The authors state that this is a very much higher proportion of pregnancy wastage than in any other group for which there are data concerning pregnancy terminations. The authors regard the birth control movement as a too single-minded limitation of fertility, and are in agreement that the decline in national fertility has been primarily due to increased use and effectiveness of contraceptives. They state there should be more emphasis on the positive aspects of birth control and more consideration of the high value of the new life.

*Philip F. Williams.*

For two centuries Sweden had a rapid population growth. Then suddenly in a land of democracy and social advances a sharp decline occurred in the birth rate. This was so steep as to cause considerable concern and when brought to the attention of the population a Commission on Population in Sweden was appointed to study the situation, a situation which is not at all peculiar to any one country. This *Report on the Sex Question*,<sup>12</sup> which is largely due to the efforts of Professor Gunnar Myrdal and Dr. Andreen-Svedberg, presents a review of the situation since 1935. The question has been studied from sex, social, political, and hygienic standpoints.

More than half of the book is devoted to the consideration of the ethical principles and evaluation of contraception. Venereal diseases and sex education are also discussed. There can be little doubt that the spread of contraception has had a marked influence in the family life of that country but the authors feel that child care and family protection are also essential facts in promoting the fertility which will be necessary to keep the population of Sweden at even a stationary level.

*Philip F. Williams.*

The second edition of this book *Modern Marriage*<sup>13</sup> by Paul Popenoe has taken cognizance of the advances of sociology and education for marriage during the

<sup>11</sup>*Controlled Fertility: An Evaluation of Clinic Service.* By Regine K. Stix, M.D., Research Associate, Milbank Memorial Fund, and Frank W. Notestein, Ph.D., Lecturer in School of Public Affairs, Princeton University. The Williams & Wilkins Company, Baltimore, 1940.

<sup>12</sup>*Report on the Sex Question.* By the Swedish Population Commission. Translated and edited by Virginia Clay Hamilton, M.D. Published for the National Committee on Maternal Health, Inc. By Williams & Wilkins Company, Baltimore, 1940.

<sup>13</sup>*Modern Marriage.* By Paul Popenoe, General Director, American Institute of Family Relations, Los Angeles, Calif., etc. Second edition, 299 pages. The Macmillan Co., New York, 1940.



and legal angles. Dr. Harry Sturgeon Crossen in presenting the surgical problem tells why articles are lost and recounts in tabular analyses 250 sponge cases, with conditions found from the time of their loss until removal, in some instances the latter being as remote as twenty-four years. After giving detailed effects of a foreign body in the peritoneal cavity, he discusses the prevention of such accidents and describes what he considers the best and safest procedure, the continuous sponge system. Similar problems regarding instruments, drains and other foreign bodies lost in the abdomen, as well as foreign bodies left in other operations, are discussed in the light of cases reported by unfortunate surgeons. He discusses the differential diagnosis, the problems of swallowed objects, x-ray visibility diagnosis, and logical methods of treatment.

In the second half of the book David F. Crossen presents the legal side of such situations. Of importance to everyone who opens the abdominal cavity are the chapters on theory of defense in sponge cases, and the basis for estimating damages to the unlucky individual in whose body the foreign substances have been overlooked at the time of operation or in drainage.

There is no doubt that a perusal of this book which states definitely the responsibilities of the operating surgeon and the decision of jurists based on actual cases will occasion a consideration of methods of preventing such surgical problems. This book deserves a place in the libraries of all hospitals and of those surgeons who open abdominal cavities. The second, or legal, part of the book should be of great value to counsellors and attorneys who are attached to medical organizations or to medical defense insurance companies.

*Philip F. Williams.*

Rodney Maingot's two-volume *Abdominal Operations*<sup>20</sup> is an important contribution to surgery. Every aspect of abdominal surgery, except the genito-urinary and the genital tracts, is covered. The introductory chapter deals with abdominal incision, its selection, as well as the technique. The author scrubs for ten minutes, which appears rather long. A very careful discussion of disruption of abdominal wounds is given. Four hundred and fifty-eight pages are devoted to the stomach and duodenum. Particularly detailed are the indications, the choice of operation, and the reason for selecting various operations. This is kept up throughout the book and adds greatly to its value. The same applies to the careful discussion of the operative techniques themselves, the dangers to be looked for, and how to avoid accidents. In pyloric stenosis of infants, Maingot advises operation if a tumor is palpable. A very detailed pre- and postoperative dietary is to be commended. In resection of the stomach, he describes six modifications of Billroth I, and classifies Billroth II as anterior and posterior Polya partial gastrectomies. He favors partial gastrectomy as the operation of choice for chronic gastric ulcer. On the other hand, in acute perforations, simple suture, when practicable, is safest. For bleeding ulcer, early operation, opening of the stomach, transfixion sutures in the affected area are preferred to resection which is advised only in special cases.

Next come operations on the spleen. A special, short chapter by L. T. Bond on sternal puncture is included. For acute pancreatitis, after every diagnostic measure has been tried, he advises operation in all uncertain cases, and in a majority of severe cases seen within the first forty-eight hours.

Very excellent chapters on the surgery of the gall bladder and bile ducts conclude the first volume. Particular attention is paid to the anomalies of the hepatic and cystic arteries.

Volume II (the paging of the volumes is continuous) deals with the liver, including injuries, abscesses, neoplasms, cysts, and also cirrhosis. The varieties of omentopexy are taken up in detail for the latter condition. In the operation for appendicitis, the author is very conservative in appendicular conditions seen in the later stages. He accepts with reservation a condition of chronic appendicitis. A very complete description of peritonitis is given, including the treatment with chemotherapy. For the treatment of inguinal hernia, he completely rejects the use

<sup>20</sup>*Abdominal Operations.* By Rodney Maingot, Senior Surgeon to the South-End General Hospital, London, etc. In two volumes, 1,385 pages with 298 illustrations. D. Appleton-Century Company, New York, 1940.

of the sections devoted to growth, development, and psychopathologic problems of childhood. These changes are in step with modern pediatric teaching which places added emphasis on the norms for physical and mental health. The charts of normal osseous development are of particular value. The discussions of pathology, usually so inadequate in a general text, deserve special commendation. It is to be regretted that more adequate sections on such everyday problems as infantile colic and cryptorchidism were not substituted for the lengthier chapters dealing, for example, with the rare congenital disturbances of ossification. Space has been conserved in this edition by the elimination of the 153 separate chapters of the previous volume. This saving has permitted the inclusion of a vastly improved bibliography. The type, although smaller than previously, is darker and more easily read. Without reservation it can be said that this book continues to be the best pediatric textbook in the field.

Alfred S. Schwartz.

The appearance of the fifth edition of Faegre and Anderson's *Child Care and Training*<sup>17</sup> indicates a continuous and widespread interest in the training of young children, with a consequent demand for information regarding development and care. This book is a fine source of factual information regarding the growth and care of the normal child. The present edition has been revised to include what the authors regard as new or valuable contributions of recent years to the subject. A valuable help for lay parents is the series of well-considered questions at the end of each chapter, while for the teacher or physician the chapter bibliography offers suggestions for collateral reading or information on specific points. There are few families which would not benefit by reading this book.

Philip F. Williams.

The fact that this little book, *Getting Ready to Be a Mother*,<sup>18</sup> has run into a fourth edition is evidence of the avidity of the lay public for good books on health education. In revising Miss Van Blarcom's book, Miss Corbin has used photographs for the entire first chapter, illustrating different events in the life of the pregnant woman and the life of the newborn baby in its first few weeks after birth. These photographs depict adequate prematernity care. In the following eleven chapters, she has discussed in a lively fashion the different things which a pregnant woman should know. These chapters are illustrated with reproductions of plaster models of Dr. Dickinson which were displayed by the Maternity Center Association at the New York World's Fair. Throughout the book the expectant mother is urged to consult her physician regarding any uncertainties, disputed points, and abnormal symptoms. There is an excellent lecture on the care and training of the newborn baby and his minor complaints. The book closes with a very philosophical bit of advice to the new mother. Each book carries with it a large baby progress chart, convenient to file in the pocket of the book so that the mother may have a permanent record of her baby's growth.

The simple language and the excellent and profuse illustrations make this one of the best manuals on the subject.

Philip F. Williams.

### Miscellaneous

The bête-noire of the laparotomists, *Foreign Bodies Left in the Abdomen*,<sup>19</sup> forms the subject of this volume in which the problem is handled from both the surgical

<sup>17</sup>*Child Care and Training*. By Marion L. Faegre, Assistant Professor of Parent Education, and John E. Anderson, Director of Institute of Child Welfare, University of Minnesota. Fifth edition, revised, 320 pages, illustrated. The University of Minnesota Press, Minneapolis, 1940.

<sup>18</sup>*Getting Ready to Be a Mother*. By Carolyn Conant Van Blarcom. Revised by Hazel Corbin, General Director of Maternity Center Association. Fourth edition, 190 pages, illustrated. The Macmillan Company, New York, 1940.

<sup>19</sup>*Foreign Bodies Left in the Abdomen*. The Surgical Problems and Legal Problems. By Harry Sturgeon Crossen, M.C., School of Medicine, Washington University, and David Frederic Crossen, LL.B., School of Law, Washington University, St. Louis. With 212 illustrations, including 4 color plates, 762 pages. The C. V. Mosby Company, St. Louis, 1940.

of New York, Paris Radium Institute with the technique used in the Mount Vernon Hospital in England. There is ample discussion of pre- and post-operative roentgen radiation not only here, but in an excellent section devoted to malignant diseases of the ovary. He states that in postoperative roentgen radiation in malignant disease of the ovary, using multiple ports of entry, treatment in four to five weeks, up to 6,000 r. to the pelvis, can be given without marked ill effects, and with only mild skin reactions.

This book is an outstanding contribution to the subject, both as a reference volume and as a practical manual for clinicians, radiologists, and pathologists. It should find a place in the libraries of all oncologists and hospitals. The book is profusely illustrated, with many color plates, and has extensive chapter bibliographies. It is an excellent example of the bookmaker's art.

Philip F. Williams.

*Sex in Development*<sup>22</sup> is a study of the growth and development of the emotional and sexual aspects of personality together with physiologic, anatomic, and medical information on a group of 153 normal women and 142 female psychiatric patients.

The work is that of a considerable number of investigators, edited by Dr. Carney Landis. The authors are well aware that they "have attempted to be objective in dealing with data based on emotionality and feeling concerning which it is difficult to be objective." Their attitude in this study has been that of empirical scientists without any attempt to prove or disprove any theory or to set up their own theories or hypothesis. Their work has been the synthesis of biographic sketches based on a controlled interview (in contradistinction to the uncontrolled psychoanalytic approach); marriage inventory; general information inventory; physical examination; vocation interest blank for women; roentgenologic studies of the pelvis; and psychiatric case history. They are well aware that the experimental psychologist will object to findings acceptable to the analyst, and vice versa.

Whether one is in agreement or disagreement with the technique used, no one can say that the approach has not been careful, thorough, and unbiased. The results, as the authors themselves realize, are not final and will be acceptable or unacceptable, depending upon the bias of the reader. They find that psychosexuality has its origin long before puberty. They likewise find that sexual aggression before puberty may be followed by homoerotic trends in adult life. They emphasize that the "most important" problem which the girl faces in adolescence is that of freeing herself from her family ties. Approximately one-sixth of the group was markedly narcissistic, about one-fourth showed some degree of masculine protest. In the abnormal group, extreme narcissism was associated with an obsessive interest in sex. They agree that surprisingly few anatomic or physiologic differences were noted between normal women and women suffering from functional mental disorders. In the psychotic groups, hypoplastic body form was more often noted. In normal women, 47 per cent of poor marital sex adjustment occurred in the group having anthropoid pelvis and in only 10 per cent of the gynecoid type. They conclude that normality can and does exist over a much wider range of developmental variation than has been thought. This interesting monograph concludes with all of the information forms used and with a tabulation of the data. It can and should be read with interest by all to whom this problem is of importance, irrespective of the reaction which it may produce.

R. T. Frank.

This research study, *Physiology of Micturition*,<sup>23</sup> by Langworthy, Kolb and Lewis should be of special interest to the gynecologist, for to him the primary

<sup>22</sup>*Sex in Development*. Edited by Carney Landis, Associate Professor of Psychology, Columbia University; Principal Research Psychologist, Psychiatric Institute and Hospital. 329 pages. Paul B. Hoeber, Inc., New York, 1940.

<sup>23</sup>*Physiology of Micturition*. By Orthello R. Langworthy, Lawrence C. Kolb, and Lloyd G. Lewis, Sub-Department of Neurology, and James Buchanan Brady Urological Institute of Johns Hopkins University. 232 pages, illustrated. Williams & Wilkins Company, Baltimore, 1940.

of injections as a method of cure. All of the operations for hernia are described most adequately. More than two hundred pages are devoted to intestinal surgery which is covered minutely. The chapter on regional enteritis is excellent.

This book is one of the most detailed, clearly conceived and carried-out descriptions of abdominal surgery that has been published. It bespeaks an unusually large experience although the author quotes practically none of his own statistics. However, he does not hesitate to express a preference for certain types of treatment or operations. The illustrations, 298 in number, with several colored plates additionally, are of a high degree of excellence. The majority are halftones, beautifully executed but somewhat dark in tone. Individual figures, numbered as a single illustration, contain from five to ten steps, and consequently the actual number of illustrations which illuminate, are four or five times the number indicated. A considerable number of line drawings and excellent reproductions of radiograms are included. The world's literature is amply and accurately represented, the actual reference being given in brackets in the text. Consequently it is a pity that the publishers did not include an authors' index.

All in all, this treatise impresses me most favorably as a book of reference for description of the diseases dealt with, as well as a very valuable guide for surgeons, both for the minute descriptions in the text as well as the accompanying illustrations.

R. T. Frank.

This imposing volume of 1,280 pages on *Malignant Disease and Its Treatment by Radium*<sup>21</sup> by Cade is divided into three parts: The first part discusses the physics of radiation. The three chapters on teletherapy, dosimetry, and the measurement of radium plaques have been written by contributors who are outstanding in their interpretation of these considerations.

The second part of the book describes the biologic effect of radiation, and the various factors which influence radiosensitivity, such as embryologic development, variety of the type of cell, environment of the tumor and such physical facts as time, intensity, and previous irradiation are explained. The author discusses the various possible mechanisms in the mode of action of radium, not only describing the effect it has on physiologic activities of the tissues but subdivides the material to discuss excitation, inhibition, and destruction. Two chapters contrast the effect of this therapeutic agent on normal and malignant tissues; the latter chapter is amply illustrated, particularly, in regard to carcinoma of the cervix to show the time variations and effects of radium. A very practical chapter on dangers of radium not only includes measures to prevent damage to normal tissues, but also brings out the possibility of carcinogenesis as in skin cancer from radium dermatitis, and the necessary care to be exercised by hospital authorities in the handling of this element.

The third part of the book reflects the clinical experiences of the author with an enormous volume of malignant disease which has passed through his hands in the Westminster Hospital and Mount Vernon Hospital in England, as well as his experiences in the Radium Institute. In the opening chapter of this third part of the book, the author discusses the limitations of surgery and the value of and principles underlying radium treatment of cancer. He then proceeds to the detailed review of malignant disease of the various body systems, describing and discussing in a very clear, logical manner the life history of various systemic malignancies, their clinical grading, diagnosis, choice of method of treatment and technique which he and others have used, and the results of treatment in his hands, as well as in other medical centers. Of particular interest to the gynecologist should be the section of approximately eighty pages devoted to malignant disease of the uterus and other structures of the reproductive canal. The outstanding work on this subject by American gynecologists is reflected in a very large number of references to American literature on the subject of carcinoma of the cervix. He contrasts the technique of the Stockholm Radiumhemmet, Memorial Hospital

<sup>21</sup>*Malignant Disease and Its Treatment by Radium.* By Stanford Cade, F.R.C.S., Surgeon, Westminster Hospital, etc. 1,280 pages, 623 illustrations, many in color. Williams and Wilkins Company, Baltimore, 1940.

tance. The chapters devoted to sulfanilamide and related sulfamide drugs are excellent, clear, and concise as is the entire text of the book. In the 73 pages devoted to the endocrines, a large amount of information, a lucid, comprehensive summary and an unbiased presentation are given.

Each chapter contains the essential historical, chemical, and physiologic basis in addition to the detailed presentation of the pharmacology, frequently illustrated by fundamental experiments. The therapy throughout is sound and conservative. The chapter bibliographies are short but comprehensive. A short chapter on prescription writing concludes the volume. In spite of the huge amount of data, the text is clear, readable, interesting and not in any way ponderous. This is a very valuable contribution with wide appeal and utility.

R. T. Frank.

This *Cyclopedic Medical Dictionary*<sup>26</sup> really is an entirely new publication and not merely a revision of Taber's previously published *Digest of Medical Terms*. It contains 1,500 pages of dictionary material with between 50,000 and 60,000 words. There are included several new features, not found in other medical dictionaries, as e.g., 16 pages, entitled "The Interpreter," of questions and terms applying chiefly to diagnosis which are given in the following five languages: English, French, German, Italian, and Spanish.

Taking its place somewhere between the large standard medical dictionary and the small, concise book prepared for nurses, Taber's dictionary should prove useful to physicians and medical students as well as to nurses.

Hugo Ehrenfest.

The rapid increase in new drugs offered on the market and far-reaching changes in endocrinologic and biologic methods of treatment have created a definite demand for a thoroughly revised and enlarged edition of the *Modern Drug Encyclopedia*.<sup>27</sup> Except for the official publication containing only those pharmaceutical products approved of by the Council on Pharmacy of the A. M. A., there is no other competent and complete source available but this Encyclopedia for authoritative information in regard to chemical constitution, action, uses, dosage, advantages or objectionable by effects of the many drugs, widely used, for oral, hypodermic, intramuscular, intravenous, vaginal and rectal application. The convenient arrangement of this immense amount of useful information has been only slightly changed in the new edition. Physician, dentist, pharmacist, and medical student, as well, will find this volume most useful in their work.

Hugo Ehrenfest.

With the aid of nine collaborators, each a recognized authority in a special field of physiology, Bard presents Macleod's famous work on *Physiology in Modern Medicine*<sup>28</sup> in a largely rewritten ninth edition. Although several new chapters have been added, others have been combined; therefore the total number has not been increased.

This volume necessarily contains much information of interest and practical importance to obstetricians and gynecologists. In particular we may refer to chapters dealing respectively with the hypophysis, the ovary, and endocrine factors in reproduction (menstruation, pregnancy, lactation, menopause, and sterility). As in previous editions the bibliography of each of the major sections is placed at the end of the volume. The index has been enlarged.

Hugo Ehrenfest.

<sup>26</sup>Taber's Cyclopedic Medical Dictionary. By Clarence Wilbur Taber, and Associates. Illustrated. F. A. Davis Company, Philadelphia, 1940.

<sup>27</sup>Modern Drug Encyclopedia. Therapeutic Guide. By Jacob Gutman, M.D., Ph.D., F.A.C.P., Director, Brooklyn Diagnostic Institute, etc. Second edition, 1,644 pages. Published by New Modern Drugs, New York City, 1941.

<sup>28</sup>Macleod's Physiology in Modern Medicine. Edited by Philip Bard, Professor of Physiology, Johns Hopkins School of Medicine. Ninth edition, 387 figures, 1,256 pages. The C. V. Mosby Company, St. Louis, 1941.

symptoms of disturbances of micturition are presented so frequently. This experimental and clinical study concerns the innervation of this smooth muscle cavity. The relation of the physiology of the bladder to lesions of the peripheral nerves, spinal cord, and brain has been investigated, discussed, and summarized. The authors point out that from their studies it seems apparent that changes occur in the bladder of pregnant women similar to those which have been observed in the ureter in pregnancy. They conclude that the increased volume of the bladder in pregnancy is dependent upon the action of progesterin. The influence of various analgesic and anesthetic agents on micturition is discussed. The section on clinical diagnosis lists illustrative cases in which disturbance has been caused by lesions of the central nervous system and various neurologic diseases.

Philip F. Williams.

When, in his introduction, an author states that his book as it appears in print is not to his entire satisfaction and when further he invites constructive criticism, he at once disarms the critic and one must read his book in the light of his modesty. However no apologies are needed by an author who possesses the scholarship shown in this book, *Bacillary and Rickettsial Infections*.<sup>24</sup>

Dr. Holmes tells us that here he has presented a book for medical students, setting forth the subject matter as he would wish it given to the student. The book covers only a limited portion of the field of the communicable diseases (not touching upon the diseases caused by viruses or by the pathogenic cocci). It runs to 630 pages of text. It contains the subject matter covered in one quarter of the course in didactic medicine at Northwestern University Medical School. It may be questioned whether the medical student can actually digest the material presented within this volume, in view of the impact of other fields which compete for his attention and must be mastered. If the student absorbs only half of the material, he will be a well-educated physician. However, if we look upon the book of Dr. Holmes as a contribution to the field of medical literature rather than purely as a textbook, we can have little to criticize.

The majority of the diseases discussed are approached historically. The history of the occurrence of the disease, the names, and the pertinent contributions of those who in the past wrote about the condition serve as fascinating introductions; therefore when the etiology, symptomatology, treatment, etc., are discussed, the disease already has a familiar aspect; and there are many points that offer possibilities for association. The usual formal presentation is not slighted and has greater interest coming as it does as a sequence to the introductory discussion.

There are interest and stimulation to be obtained in reading the pages of this book. There is evidence of wide knowledge and long and painstaking study by the author without pedantic presentation.

Moyer S. Fleisher.

Goodman and Gilman's *The Pharmacological Basis of Therapeutics*<sup>25</sup> is, in the best sense of the word, a textbook of pharmacology, toxicology, and therapeutics. Its content is far too encyclopedic to permit of detailed review; its scope embraces anatomy and chemistry also. The book is designed for physicians and students; its appeal, however, should include investigators in all branches of science.

The arrangement is admirable—central nervous depressants and stimulants, local anesthetics, drugs acting on autonomic effector cells, cardiovascular drugs, etc.; drugs acting locally on the skin and mucous membranes; antiseptics, disinfectants and drugs used in chemotherapy of infectious diseases, drugs of endocrine origin and the vitamins are sections here selected for comment because of their impor-

<sup>24</sup>*Bacillary and Rickettsial Infections. Acute and Chronic.* By William H. Holmes, Professor of Medicine, Northwestern University Medical School, Chicago, etc. 676 pages. The Macmillan Company, New York, 1940.

<sup>25</sup>*The Pharmacological Basis of Therapeutics.* By Louis Goodman, M.A., M.D., Assistant Professor of Pharmacology and Toxicology, Yale University, School of Medicine, and Alfred Gilman, Ph.D., Assistant Professor of Pharmacology and Toxicology, Yale University, School of Medicine. 126 figures, 1,383 pages. The Macmillan Company, New York, 1941.

Sammartino<sup>32</sup> practices dilatation of the sphincter ani with one, two, or more fingers preliminary to abdominal palpation in inflammatory and other acute and chronic conditions of the abdomen. By this measure he claims to facilitate localization and diagnosis. His claims are based on the study of 400 cases of various abdominal diseases.

R. T. Frank.

The third series of Surgical Monographs by Branco Ribeiro<sup>33</sup> deals with diverse surgical subjects. Of interest to our readers are a report on appendicitis during pregnancy (report of one case, considerable statistical literature). Also a report of large uterine myoma (weight 13 kg.).

R. T. Frank.

Zuckermann in his *Surgical Treatment of Constipation*<sup>34</sup> appears to be a disciple of Lane. He concedes that the majority of patients should be treated by hygienic, dietetic, physiotherapeutic, and drug measures. Surgery should be limited to persistent, rebellious forms in which the radiographs show marked retardation of the fecal column and to patients in whom toxemia and pain are manifest. Such measures as colopexy, various entero- and coloanastomoses are described most sketchily. His main theme, however, is abdominal ganglionectomy which he depicts in detail. The literature from 1923 to 1936 is given in abstracts. The histories of twenty patients on whom various types of ganglionectomies were performed by the author, form the main text.

R. T. Frank.

<sup>32</sup>La Maniobra Ano Parieto-Abdominal En Los Procesos Agudos Del Abdomen. Por Dr. Emilio S. Sammartino. El Ateneo, liberia y editorial. Buenos Aires, 1940.

<sup>33</sup>Estudos Cirurgicos. By Eurico Branco Ribeiro, Director do Sanatorio São Lucas. 219 pages, illustrated. Sociedade Editora Medica Limitada, São Paulo, Brasil, 1940.

<sup>34</sup>Cirugia de la Constipacion. Par el Dr. Conrado Zuckermann, Professor de patologia quirurgica de la facultad de medicina de Mexico. Con 32 grabados. Mexico, 1939.

*L. Emmett Holt, Pioneer of a Children's Century*<sup>29</sup> was both an idealist and a man of action. In this delightfully written story of his life by Mr. Duffus and Dr. Holt, Jr., one learns of Holt's decision to study medicine, his various experiences in anatomy, surgery, and general practice until he ended up in his final choice of children's diseases. From that point on there was hardly a step in the development of American pediatrics in which he did not take an active part—the establishment of the Babies Hospital; publication of his two books, one for the laity and one for the physician, both best sellers; his influence in helping to establish the Rockefeller Institute; his association with the Milk Situation; all are beautifully described. His contacts with laboratory, research, literature, national problems, post-war situations in Europe, and medical organizations show what a tremendous vitality this man possessed. Letters which he wrote from China just before his death reveal that his intense interest in the problems of children kept up until the last minute. This is a fine example of medical biography.

*Philip F. Williams.*

In the evening of a long and useful life, Dr. Wolf recounts his early days in Germany and his practice in Kansas City in a most interesting medical biography entitled *A Family Doctor's Notebook*.<sup>30</sup> The recollections of a man who at seventy-five years looks back over some fifty years of practice and thirty-five years of teaching not only makes an interesting history of the practice of medicine in the United States, but gives many personal opinions of the social trend in the present and past decades. Dr. Wolf has well described the place of the physician in relation to the patient, his brother physician and civic activities. Among his philosophic essays on present-day topics are two interesting chapters on the high cost of doctoring and medical economics in which Dr. Wolf very ably pleads the case for the physician. He closes the book with a chapter which reflects pride in the past accomplishments of the medical profession while looking forward to greater discoveries of future days. These observations and essays merit wide reading by physician and layman.

*Philip F. Williams.*

Dr. Minnitt has taken over the revision of this book *Ross and Fairlie's Handbook of Anaesthetics*,<sup>31</sup> upon the deaths of the former authors. Much of the material in this fifth edition is stated to have been re-written, while three additional chapters have been added. The first one is on "Cyclopropane and Closed Circuit CO<sub>2</sub> Absorption Anaesthesia." The second new chapter is devoted to the "Therapeutic Use of Oxygen, Helium, and Carbon Dioxide" and in this chapter, particularly, there occurs the discussion of treatment of postoperative complications by these agents, as well as the use of oxygen tents.

In discussing anesthesia in obstetrics, Dr. Minnitt recounts his personal experiences with chloroform, which is not largely used in the United States. He gives an excellent recapitulation of various methods for producing amnesia and analgesia during labor, and describes an apparatus for the use of gas analgesia in the home labors. He advocates a wider employment of local anesthesia for cesarean section, and the avoidance of chloroform for the major vaginal operations. This compact presentation of the subject should be a useful guide to students and practitioners of anesthesia.

*Philip F. Williams.*

<sup>29</sup>*L. Emmett Holt, Pioneer of Children's Century.* By R. L. Duffus and L. Emmett Holt, Jr. Foreword by Edwards A. Park, Professor of Pediatrics, Johns Hopkins University. Illustrated, 295 pages. D. Appleton-Century Company, New York, 1940.

<sup>30</sup>*A Family Doctor's Notebook.* By I. J. Wolf, M.D., Professor of Medicine, Emerit. University of Kansas School of Medicine. Fortuny's, New York City, 1941.

<sup>31</sup>*Handbook of Anaesthetics.* Revised by R. J. Minnitt, M.D., Lecturer in Anaesthesia, University of Liverpool, etc. With chapters on local and spinal anaesthesia by W. Quarry Wood, M.D., Surgeon, Edinburgh Royal Infirmary. Fifth edition, 103 illustrations, 364 pages. Williams and Wilkins Company, Baltimore, 1940.



# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Cesarean Section

Heard, Kenneth M.: *Anesthesia in Cesarean Section*, Surg., Gynec. & Obst. 70: 657, 1940.

In the literature on cesarean section, very little mention is made of the anesthetic and even less of its effect upon the respirations of the infant. When artificial respiration is needed or pneumonia follows initial respiratory difficulties, it is too often dismissed as due to toxemia or other ill health in the mother. In reality, the type of anesthetic used for the operation plays a very definite part in the baby's start in life. No form of anesthesia nor method of resuscitation will save a baby with a very marked defect of brain or heart. It is doomed by congenital defects for which there is no remedy. Many others, however, fail to survive the first few hours because their respiratory mechanism is unable to function properly, due to depression by an anesthetic or sedative. It is impossible to anesthetize or sedate the mother by inhalation or narcotics without anesthetizing the fetus. The drug is absorbed at the time when the fetal respiratory and cardiac centers are at their lowest ebb, following prolonged labor or damage secondary to maternal ill health. Most babies, particularly if the operation is at the time of election, will withstand this terminal depression and breathe spontaneously. The occasional one, however, is unable to cope with the depressing effect of the anesthetic and breathes only after resuscitation. Too often the respirations remain unsatisfactory, and atelectasis leads to pneumonia or death. Since it is impossible to predict in advance the exact state of the respiratory system, safety demands the use of the anesthetic which will add least strain to the already overburdened fetus. The anesthesia in question in this series proved to be spinal with straight cyclopropane-oxygen, or nitrous oxide-oxygen without ether a close second. Ether is definitely contraindicated, particularly after a heavy sedative.

WILLIAM C. HENSKE.

Synephias, M.: *Spinal Anesthesia With Percain and Cesarean Section*, Rev. franç. de gynéc. et d'obst. 34: 162, 1939.

During the past three years, 67 cesarean sections were performed at the Strasbourg Clinic under spinal anesthesia with percaine and 19 additional cesareans were done under ether anesthesia. Synephias compares the three forms of anesthesia used for cesarean section, namely, general, local, and spinal.

Among the general anesthetics used are ether, evipan, and gas. Ether is toxic, it produces disagreeable postoperative effects, and it may be harmful to the child. Evipan has resulted in many accidental deaths. Thus, Menegaux reported 22 deaths and Synephias collected six serious accidents and 20 deaths during short operations performed under evipan. Danger to the fetus is not excluded because of the permeability of the placenta to the barbiturates.

Gas in the form of nitrous oxide, ethylene, and cyclopropane is a distinct advance in general anesthesia, because in over 4,000,000 gas anesthetics there has not been a single death. However, gas anesthesia requires cumbersome and expensive apparatus and the services of a special anesthetist. Furthermore, they are explosive and they have a bad effect on the contractility of the uterus.

## Society Transactions

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### SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

*THIRD ANNUAL MEETING, JACKSONVILLE, FLA.*

*FEBRUARY 7 AND 8, 1941*

The following papers were presented:

**Placenta Bilobata.** Drs. Richard Torpin, Augusta, Ga., and B. F. Hart, Winter Park, Fla. (For original article, see page 38.)

**Sterilization in the Puerperium.** Drs. W. N. Thornton, Jr., and T. J. Williams, University, Va. (For original article, see page 54.)

**Benjamin Rush, Obstetrician.** Dr. M. Pierce Rucker (President's Address) Richmond, Va.

**Placenta in Late Toxemia of Pregnancy.** Dr. R. A. Bartholomew, Atlanta, Ga.

**Acute Polyhydramnios.** Dr. J. D. Parker, Greenville, S. C.

**Acute Appendicitis in Pregnancy.** Dr. C. D. Hoffman, Orlando, Fla.

**The Excretion of Estrogenic and Androgenic Substances by Intra-Human Primates.** Dr. William C. Young, New Haven, Conn.

**The Role of the Maternity Home in Treating the Low Income Group.** Dr. J. M. Hoffman, Pensacola, Fla.

**Supravaginal and Total Hysterectomy.** Dr. Richard L. Pearse, Durham, N. C. (For original article, see page 22.)

**A Study of 150 Consecutive Cases of Ectopic Pregnancy.** Dr. H. H. Ware, Jr., and W. C. Winn, Richmond, Va. (For original article, see page 33.)

**Oral Progestin (Anhydro-Hydroxy-Progesterone) in the Treatment of Dysmenorrhea.** R. B. Greenblatt, E. McCall, and R. Torpin, Augusta, Ga. (For original article, see page 50.)

The guest speakers were Dr. John Rock, Boston, Mass.; Dr. William C. Young, New Haven, Conn.; and Dr. N. J. Eastman, Baltimore, Md.

Weaver, R. T.: *Changing Conditions for Cesarean Section*, *Canad. M. A. J.* 40: 259, 1939.

A review of the literature reveals a wide variation in the incidence of cesarean section with a definite tendency toward an increase. In some areas, 33 per cent of maternal deaths have occurred following cesarean section delivery. In 4,694 cases collected from the literature, the indications for operation were as follows: cephalopelvic disproportion, 44.6 per cent; previous section, 15.2 per cent; placenta previa, 6.6 per cent; accidental hemorrhage, 2.9 per cent; late toxemias, 9.1 per cent; cardiac disease, 3.9 per cent; and miscellaneous, 12.0 per cent.

A discussion of these indications shows that there are considerable differences of opinion among various authors. Weaver believes that cesarean section must be looked upon as the most dangerous of all abdominopelvic operations and that the nursing and medical professions and the public must realize that abdominal delivery is not the solution for every obstetric problem.

CARL P. HUBER.

Howkins, John: *Pelvimetry and the True Conjugate*, *Brit. M. J.* 1: 278, 1938.

The author feels that cesarean sections are recommended, too often, on the basis of the often erroneous conclusion that, if the sacral promontory can be felt per vaginam, the patient has a contracted pelvis. He explains that three factors have to be taken into account, namely, first, the length of the true conjugate; second, the effective length of the examining finger; and, third, the rigidity of the vaginal introitus, which depends largely upon the cooperative relaxation of the patient and on her parity.

He concludes that clinical measurement of the true conjugate can be done in normally sized pelvis when good cooperation is obtained and the examiner has had practice and is skillful. He also points out that when the diameter is truthfully obtained it is open to considerable error in addition to that due to the particular anatomy of a given patient, such as the depth and inclination of the symphysis.

F. L. ADAIR AND JOHN A. HAUGEN.

Johnston, H. W.: *The Termination of Pregnancy Before the Period of Viability by Abdominal Hysterotomy Through the Lower Uterine Segment*, *Canad. M. A. J.* 43: 552, 1940.

The premature termination of pregnancy after the third month by abdominal hysterotomy through the lower uterine segment is described. The author prefers this procedure because the incision is covered by the peritoneum of the bladder flap and adhesions which may follow the usual high incision are prevented. The uterine incision may be made either longitudinally or transversely.

CARL P. HUBER.

Anderodias, J., and Pery, G.: *The Indications for Low Cesarean Section in Amniotic Infections*, *Rev. franç. de gynéc. et d'obst.* 34: 1, 1939.

The purpose of this paper is to show that the low cervical cesarean section may be performed in cases which formerly would have been subjected to mutilating operations. Among 85 instances there were five fatal cases where the membranes had ruptured some time before the operation (6, 8, 8, 46, and 48 hours, respectively). The longer the bag of waters was ruptured the greater the risk of the operation.

In cases of definite amniotic infection, the authors employ the low operation but they sew the abdominal wall in one layer instead of three. They claim by this measure to avoid dead spaces which would be filled by hematomas which become infected and produce abscesses of the abdominal wall. Among 15 patients operated upon in this way, there were no failures.

Among the 83 women operated upon while they had a temperature above 37.5° C., there were 5 deaths (5.8 per cent). The causes of death were septicemia (2), peritonitis, cellulitis of the broad ligament and myocarditis. Infections manifested

Local anesthesia is excellent and innocuous, but it is painful when used in women who are having violent uterine contractions. It is practically useless in cases of cesarean section where the uterus is exteriorized.

Spinal anesthesia is simple, it has a favorable action on uterine contractions and therefore diminishes bleeding, it permits easy exteriorization of the uterus and has no harmful effect on the child. However, it may be dangerous, because spinal anesthesia increases in risk the nearer a pregnant woman is to term.

J. P. GREENHILL.

Feldweg, P.: *The Position of Cesarean Section in Obstetrics*, Zentralbl. f. Gynäk. 63: 1511, 1939.

The cesarean section results for the last five years in the author's clinic are studied and reported. There were 205 sections and about 3,300 deliveries from below, with no maternal section deaths but with 8 fetal deaths. These results are then compared with those of delivery from below. When other than spontaneous delivery occurred, but where delivery was accomplished from below, there was a maternal mortality of 1.32 per cent, comparable to the expected mortality of cesarean section. A brief summary of the histories of the patients who died after delivery from below leaves no doubt but that cesarean section was either not indicated or would not have changed the outcome. The author concludes that, as it is applied in his clinic, an extension of the indications for section from the standpoint of the welfare of the mother is not justified.

He then examines the fetal mortality. Spontaneous delivery, operative delivery from below, and section carried 2.9 per cent, 13.9 per cent, and 3.8 per cent fetal mortality, respectively. The cesarean section mortality is weighted with several mistaken diagnoses (fetal abnormality, unrecognized prematurity, etc.) which lead him to believe that this can be reduced. He concludes that some extension of cesarean section on the basis of fetal welfare is justified, particularly in view of the very low maternal mortality of the operation. Against this, he places what he believes to be a lowered fertility rate in patients upon whom section has been done.

The indications for section are those generally accepted so far as can be determined from the brief statements. Two of these will not find acceptance however. Eclampsia and previous section accounted for more than 50 of the reported operations. No section is done after a vaginal examination of any sort and whether done in his own clinic or elsewhere. All of his sections are done under local anesthesia, and he makes a strong plea for this procedure. A transverse uterine incision is made without elevating the bladder.

As in all German clinics, the author has given much consideration to the problem of embolism. It will perhaps be a shock to most physicians in this country to read that the patient is made to get up from the operating table and walk. Every day thereafter the patient is gotten up and walks. No bad results have been seen (Pfannenstiel's incision of the abdominal wall is used), and there were no embolus deaths in the series.

In conclusion, the author lays down five rules which are the most important factors in cesarean section results. These are worth repeating.

1. Exclusion of all infected patients, as well as those who have had vaginal operations or vaginal examinations (presumably during labor).
2. Avoidance of all alkaloids (before delivery of the child) and all anesthetic agents which have a central effect.
3. The use of only local anesthesia.
4. Transverse incision of the abdominal wall and curved transverse incision of the uterus.
5. Get the patient up and about from the operating table and every day thereafter.

Some of the statements will not find general agreement in this country, but the paper gives one the impression of a clear-headed presentation of the problem and will repay reading in the original.

J. L. MCKELVEY.

without exteriorization; the intestines are not in contact with the field of operation and the operation may be performed by any physician who can do surgery.

J. P. GREENHILL.

**Fuchs, H.:** Labor After Cesarean Section, Particularly After the Arc Incision in the Isthmus, *Zentralbl. f. Gynäk.* 61: 2578, 1937.

In the 245 cases of low cesarean section performed, the maternal mortality was 1.6 per cent. In this group 46 women were subsequently delivered by cesarean section, but 19 had vaginal deliveries. There was no mortality in this group. At the time of the repeated cesarean operation, the scar was carefully examined. In 33 cases no scar was visible, in 10 there was a slight thinning of the scar area, and in 3 cases there was a pathologic thinning. In 5 cases pieces of tissue were removed for microscopic examination. The author believes that the danger of rupture of the uterus after the low operation is considerably less than after the classic operation. Nevertheless even women who have cervical operations must be carefully watched in subsequent labors because the scar may thin out and rupture subperitoneally.

The author recommends that in all subsequent cesarean sections, the operator should carefully inspect the area of the previous scar and correlate it with the stage of labor. He should also remove a piece of tissue for histologic study. The only investigation reported of the histologic study of uterine scars after cervical cesarean sections is that of Greenhill and Bloom. More such studies are needed. The author also suggests that in cases of vaginal delivery after cesarean section, the physician should examine the isthmus of the uterus.

J. P. GREENHILL.

**Repetti, Mario:** Strength of the Uterine Scar Following Cesarean Section, *Folia demograph.-gynaec.* 37: 159, 1940.

The author describes a case of spontaneous rupture of the uterus in the beginning of labor in a woman who had had two previous cesarean sections. One was of the fundal type and the other in the lower segment. The rupture occurred in the first fundal incision where the placenta had attached. The writer discusses the frequency, etiology, pathogenesis, and pathology of rupture of the uterus following previous cesarean section. In general, authors prefer the lower segment incision. In conclusion, it is the writer's opinion that even in the absence of any sign of abnormality in the puerperium, whether the incision was fundal or segmental, one cannot prognosticate as to whether the scar will hold or not.

MARIO A. CASTALLO.

**Nicoletti, Guido:** The Fate of the Cesarean Section Scar, *Rassegna d'ostet. e ginec.* 48: 165, 1939.

The author describes the histology of a uterine scar one year after cesarean section. At this time the uterus was removed with the adnexa because of ovarian malignancy.

The author states that the uterine wounds of cesarean sections heal only by secondary intention. The best prophylaxis to good uterine scar formation is dependent upon the accuracy of the anatomic reconstruction of the uterine wound. A poorly reconstructed uterine wound in the fundal region will logically be more liable to rupture from the less well-formed scar.

CLAIR E. FOLSOME.

**Rickards, C. E. B.:** Uterine Rupture Following Caesarean Section, *Brit. M. J.* 1: 1359, 1938.

Rupture of the uterus following a previous cesarean section may occur during pregnancy or during labor, especially if the latter is obstructed. The author classifies such ruptures into five groups, and furnishes case histories and characteristics of each group.

themselves after operation in 22 cases and consisted of the following: unilateral phlebitis (6), bilateral phlebitis (2), abscess of abdominal wall (6), pulmonary complications (5), and endometritis (3). The total fetal mortality was 7 per cent.

During the last ten years, the total number of cesarean sections performed was 280. There were 9 maternal deaths, an incidence of 3.2 per cent.

J. P. GREENHILL.

Lorier, V. L.: *My Experience With the Cesarean Operation*, *Rev. franç. de gynéc. et d'obst.* 34: 285, 1939.

This paper is based on 277 cesarean sections performed in the author's clinic. Of this number 11 were classic cesarean sections and 166 were cervical operations. Among the classic cesarean cases the death rate was 9 per cent; whereas in the cervical group it was only 3.6 per cent. In the group of classic operations, the maternal mortality was 3.9 per cent for the patients with intact membranes, but it was 16 per cent for those with ruptured membranes. In the low cervical group, the figures were 5.1 and 5.7 per cent, respectively. The fetal death rate for the classic sections was 5.4 per cent and for the low operations it was 4.8 per cent. The author believes that the low cervical operation is the one of choice.

J. P. GREENHILL.

Courtois, J., and Bouchacourt, C.: *Concerning 158 Low Cesarean Sections. Indications and Results, and Opportune Time for Operating*, *Rev. franç. de gynéc. et d'obst.* 33: 790, 1938.

In a series of 205 cesarean sections performed by Courtois and Bouchacourt, 158 were of the low cervical type. The indication in 113 cases was contracted pelvis, and in this group there were 7 maternal deaths (6.19 per cent) and five fetal deaths (4.42 per cent). Among the remaining 45 cervical operations performed for a variety of indications, there were three maternal fatalities (6.8 per cent). Hence, the total maternal mortality was 6.32 per cent and the total fetal death rate was 5.06 per cent. In this series there were 16 low cervical operations in women who were more or less infected and the death rate in this group was 18.7 per cent. On the other hand, the death rate in the clean cases was only 3.5 per cent. The maternal mortality for the patients not in labor was 6.25 per cent; for those at the beginning of labor, it was 2.94 per cent; for those late in labor, it was 10 per cent; and for a few in whom the operation was performed after a very long labor, it was 33.3 per cent.

The authors conclude that the optimum time for performing a cesarean section is at the beginning of labor, because at this time the best results for both mother and baby are obtained. It is preferable to operate shortly after the bag of waters has ruptured. For the mother, the twentieth hour of labor is a dramatic pivotal point, because after this the risks of the operation increase very markedly. Infants have less resistance than their mothers; hence, in cases of dystocia, the tenth hour should be considered the dead line, especially if the membranes have ruptured. The low cervical cesarean section has a distinct maternal mortality regardless of the indication, the condition of the mother and the skill of the operator.

J. P. GREENHILL.

Serdukoff, M. G.: *Advantages of the Transverse, Transcervical and Retrovesical Incision in Cesarean Section*, *Gynécologie* 38: 463, 1939.

In the opinion of Serdukoff, the lower uterine segment is far preferable to the body of the uterus for making the incision in cesarean section. The transverse incision in the lower uterine segment has the following advantages over the vertical incision: The risk of interstitial hemorrhage is less; the coaptation of the tissues is more perfect; the scar heals better because the lower uterine segment is at rest; there is better peritonization which is important in the prevention of adhesions; the obstetrician has more room for the extraction of the fetus; the uterus is opened

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Candidates certified (total 227) by American Board of Obstetrics and Gynecology at the June, 1941, meeting held at Cleveland, Ohio:

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|---|--|
| ARCHIE A. ABRAMS, Boston, Mass.                   | JAMES L. CROSSLEY, Watertown, N. Y.          |
| GERHARD AHNQUIST, New York, N. Y.                 | J. H. CURHAN, Detroit, Mich.                 |
| RUDOLPH F. AMYOT, Cohoes, N. Y.                   | AUGUST F. DARO, Chicago, Ill.                |
| I. ANDRUSSIER, Philadelphia, Pa.                  | ARTHUR M. DAVIDS, New York, N. Y.            |
| J. MARSH ALESBURY, Philadelphia, Pa.              | C. S. DAY, Cedar Rapids, Ia.                 |
| B. R. AUSTIN, Pittsburgh, Pa.                     | RUSSELL DEALVAREZ-SKINNER, Ann Arbor, Mich.  |
| JOHN M. BAILEY, Evanston, Ill.                    | JACOB F. DEICH, Boston, Mass.                |
| D. M. BALDWIN, Jacksonville, Fla.                 | A. J. DE PINTO, Phoenix, Ariz.               |
| GEMMA BARZILAI, New York, N. Y.                   | C. C. DRAA, Chicago, Ill.                    |
| D. S. BAYER, Nashville, Tenn.                     | PAUL V. DUFFY, Cleveland, Ohio.              |
| JACOB S. BEILLY, Chicago, Ill.                    | RICHARD B. DUNN, Greensboro, N. C.           |
| JERRELL BENNETT, Fort Worth, Tex.                 | JAMES A. DUSBABEK, Washington, D. C.         |
| JAMES BERCEY, Milwaukee, Wis.                     | ELEANOR B. EASLEY, Durham, N. C.             |
| SAUL BERMAN, Boston, Mass.                        | EDUARD EICHNER, Cleveland, Ohio.             |
| BERNARD J. BERNSTINE, Philadelphia, Pa.           | EUGENE T. ELLISON, Greenville, Miss.         |
| H. L. BISKIND, Cleveland, Ohio                    | HERMAN L. ENSELBERG, Long Island City, N. Y. |
| WILLIAM T. BLACK, JR., Memphis, Tenn.             | WILLIAM A. EPSTEIN, Brooklyn, N. Y.          |
| ROY V. BOEDEKER, St. Louis, Mo.                   | FRANK X. FAGAN, Hartford, Conn.              |
| S. M. BOLTUCH, New York, N. Y.                    | MORRIS FERESTEN, New York, N. Y.             |
| EDWARD J. BOMZE, Chicago, Ill.                    | JOSEPH D. FERRONE, Boston, Mass.             |
| BENJ. F. BORNSTEIN, Boston, Mass.                 | WILLIAM M. FINDLEY, New York, N. Y.          |
| LESTER J. BOSSERT, Cincinnati, Ohio               | CHARLES FINKELSTEIN, Chicago, Ill.           |
| H. E. BOWLES, Honolulu, T. H.                     | ARTHUR FIRST, Philadelphia, Pa.              |
| JOHN H. BOYD, New York, N. Y.                     | JOHN M. FLEMING, Spartanburg, S. C.          |
| HARRY BENARON, Chicago, Ill.                      | FRANCIS FORD, Rochester, N. Y.               |
| JAMES P. BOYLAN, New York, N. Y.                  | LEON FOSTER, St. Louis, Mo.                  |
| PETER L. BOYLE, Youngstown, Ohio                  | HENRY FREEDMAN, Brooklyn, N. Y.              |
| HARRY BOYSEN, Chicago, Ill.                       | IRVING FRIEDMAN, New Haven, Conn.            |
| P. N. BRAY, Duluth, Minn.                         | CHARLES W. FROATS, St. Paul, Minn.           |
| JAMES X. BREMNER, Chicago, Ill.                   | LOUIS B. FOURNIER, Syracuse, N. Y.           |
| ADDISON W. BROWN, Des Moines, Iowa                | SPRAGUE GARDINER, Baltimore, Md.             |
| WILLIAM H. BROWNFIELD, Los Angeles, Calif.        | FERDINAND GAENSBAUER, Pontiac, Mich.         |
| ENDRE K. BRUNNER, New York, N. Y.                 | DANIEL J. GEARY, Morristown, N. J.           |
| GORDON BURNS, Chicago, Ill.                       | WILLIAM W. GIBBS, Chicago, Ill.              |
| HERBERT BURWIG, Buffalo, N. Y.                    | C. S. GLISSON, Ft. Bragg, N. C.              |
| NANCY D. CAMPBELL, Las Vegas, N. M.               | MILTON GOLDBERGER, Providence, R. I.         |
| WM. D. CARRELL, Tucson, Ariz.                     | ARTHUR V. GREELEY, New York, N. Y.           |
| MILTON A. CARVALHO, Binghamton, N. Y.             | ROBERT B. GREENBLATT, Augusta, Ga.           |
| G. R. CHEATHAM, Endicott, N. Y.                   | LUCIAN S. GRIFFITH, Grand Rapids, Mich.      |
| LAURENCE A. CHROUCH, Detroit, Mich.               | J. E. GRIFFITHS, Bryn Mawr, Pa.              |
| BERNARD L. CINBERG, New York, N. Y.               | W. F. GUERRIERO, New Orleans, La.            |
| JACOB CLAHR, New York, N. Y.                      | CHARLES A. GWYNN, Syracuse, N. Y.            |
| C. LOUISE CLANCY, Chicago, Ill.                   | MERIT D. HAAG, Toledo, Ohio.                 |
| B. F. CLARK, St. Johnsbury, Vt.                   | RAYMOND C. HALL, San Diego, Calif.           |
| FRANK J. CLARKE, Forest Hills, Long Island, N. Y. | HUGH G. HAMILTON, Kansas City, Mo.           |
| ARTHUR J. CONNOLLY, New Haven, Conn.              | SAMUEL HANSON, Stockton, Calif.              |
| KENNETH E. COX, Kansas City, Mo.                  | BERNARD HARK, Philadelphia, Pa.              |
| ROBERT L. CRAIG, New York, N. Y.                  |  |

All patients who have had a previous cesarean section should have subsequent confinements under skilled supervision and have access to a fully equipped operating theater. If the indication for cesarean section is absolute, the operation should be performed during the last week of pregnancy or at the onset of labor. Unnecessary delay in these cases may lead to rupture of the uterus. The patient must be carefully supervised during the latter part of pregnancy and abnormal symptoms, i.e., lower abdominal pain, must be regarded with suspicion.

F. L. ADAIR AND S. A. PEARL.

**Fournier, R.: Insurmountable Dystocia Caused by a Scar of a Transverse Low Cesarean Section, Gynécologie 38: 5, 1939.**

The incidence of rupture of the uterus following the cervical cesarean section in which the longitudinal incision is used is about 0.28 per cent. The scar itself does not produce any dystocia during labor. On the other hand, Fournier reports a case of cervical cesarean section in which a transverse incision was used. In this case, the well-healed scar produced such serious obstruction to the descent of the fetal head that a rupture would certainly have occurred in the lower uterine segment if a hysterectomy had not been performed. At operation, after opening the uterus, a thick shelf of muscle was found preventing descent of the head. This was in the region of the transverse incision of the low cesarean section. After removal of the baby, the uterus contracted, and it was seen that the previous scar divided the uterus into two parts, a lower part with a thin, flaccid wall and an upper part with a very thick wall about three times the thickness of the lower part. There was no transition between the two parts but a sudden sharp change.

J. P. GREENHILL.

**Arthure, H.: Rupture of a Cesarean Scar Treated by Simple Drainage and Followed by Pregnancy, Lancet 2: 19, 1938.**

A case is reported in which unrecognized rupture of a classical cesarean scar occurred during the thirty-sixth week of pregnancy with extrusion of the fetus into the abdomen. Ten weeks later, following attempts at bougie induction of labor, laparotomy was performed. The macerated extrauterine fetus, lying anterior to a rupture in the uterus, was removed and the wound drained. Two years later in a subsequent pregnancy, laparohysterotomy and sterilization were performed. The site of rupture could not be seen, and there was only one omental adhesion to the uterus.

The author has been unable to find other reports of pregnancy subsequent to rupture of the uterus which was treated by drainage.

CARL P. HUBER.

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## Items

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### American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 3, 1942, at 2:00 P.M. Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

Applications for admission to Group B, Part I examinations must be on file in the Secretary's Office not later than October 6, 1941. Group A applications must be received in the Secretary's Office not later than March 1, 1942.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Atlantic City, N. J., immediately prior to the 1942 meeting of the American Medical Association.



BENNO TUNIS, Newark, N. J.  
 THOMAS R. TURINO, Brooklyn, N. Y.  
 FELIX H. VANN, Englewood, N. J.  
 MEYER VITSKY, Richmond, Va.  
 RUDY F. VOGT, Louisville, Ky.  
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 JOHN A. WALL, Houston, Texas  
 RAYMOND A. WALLACE, Memphis, Tenn.  
 ROBERT I. WALTER, New York, N. Y.  
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WILLIAM C. WEIR, Cleveland, Ohio.  
 P. FRANCIS WEISS, Boston, Mass.  
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 THEODORE W. WELLER, Oakland, Calif.  
 BENJ. B. WETCHLER, Fort Bragg, N. C.  
 JOHN WHITRIDGE, JR., Baltimore, Md.  
 S. W. WILLIS, Bronxville, N. Y.  
 LEO WILSON, New York, N. Y.  
 MAUDE HALL WINNETT, Chicago, Ill.

## The Second American Congress on Obstetrics and Gynecology

The Second American Congress on Obstetrics and Gynecology will be held in St. Louis, Missouri, April 6 to 10, 1942. All of the meetings and both the Commercial and Educational and Scientific Exhibits will be held in the Municipal Auditorium.

The various committees have been set up and the following Chairmen have been appointed:

Executive Committee	DR. FRED L. ADAIR, Chicago
Program Committee	DR. E. D. PLASS, Iowa City
Motion Picture Committee	DR. ROBERT D. MUSSEY, Rochester
Educational and Scientific Exhibits	DR. H. CLOSE HESSELTINE, Chicago
Commercial Exhibits	DR. PHILIP F. WILLIAMS, Philadelphia
Lay Publicity	DR. JOSEPH L. BAER, Chicago
Professional Publicity	DR. GEORGE W. KOSMAK, New York
Publications Committee	DR. GOODRICH C. SCHAUFFLER, Portland
Evening Meetings	DR. ROBERT L. DENORMANDIE, Boston
Membership Committee	DR. BUFORD G. HAMILTON, Kansas City
Budget and Finance Committee	DR. WILLIAM C. DANFORTH, Evanston

The general plan for the program will be much the same as that of the first Congress, which was held in Cleveland, Sept. 11 to 15, 1939, with sectional meetings for the various groups (nurses, public health, administrators, educators, and physicians), general sessions for all members attending the Congress and round tables. There will be evening sessions open to the general public.

Adequate time for registration will be given the first day, before the opening of the sessions of the Congress. Admission to the Congress will be by individual membership card only. These may be secured by payment of the five dollars registration fee, any time after Sept. 1, 1941.

At the suggestion of the Medical Exhibitors Association, more time will be allowed for the members of the Congress to visit the Exhibits. The response to a letter sent to the firms handling products of interest to our group telling them of a second Congress has been excellent and we are assured of an excellent Commercial Exhibit.

The hotel headquarters have not been assigned to the various groups as yet, but the Medical Section and General Congress Headquarters will be in the Jefferson Hotel.

For further information, apply to the Chicago office of the Congress, 650 Rush Street.

## Erratum

In the article, "Jelly Contraceptives," by Dr. Irving F. Stein, which appeared in the May, 1941, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, p. 853, lines 21 and 22, it is stated that Stix has shown that the diaphragm and jelly method is only 76 per cent effective in relief recipients. This figure should be corrected to read 85 per cent.

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 A. HIRSHEIMER, Dayton, Ohio.  
 RALPH L. HOFFMAN, San Diego, Calif.  
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 OLIVER E. TODD, Toledo, Ohio.  
 CLARENCE E. TOSHACH, Saginaw, Mich.  
 ALEX A. TULSKY, Fort Benning, Ga.

- Washington Gynecological Society.** *President*, R. L. Sylvester. *Secretary*, W. R. Thomas, 1830 K. Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, E. Lee Dorsett. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Galveston, Texas, September, 1941.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, Russell W. Alles. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Francis R. Irving. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, T. M. Boulware, Birmingham, Ala. *Secretary*, Eva F. Dodge, 519 Dexter Avenue, Montgomery, Ala. Next meeting, Mobile, Ala., April, 1941.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.

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## Books Received

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**THE MASK OF SANITY.** By Hervey Cleckley, professor of neuropsychiatry, University of Georgia School of Medicine. 1941. The C. V. Mosby Company, St. Louis.

**ESSENTIALS OF GYNECOLOGY.** By Leo Brady, assistant professor of gynecology, University of Maryland, etc., and Ethna Louise Kurtz, R.N., head nurse, Brady Urologic Institute, Johns Hopkins Hospital, etc. 57 illustrations, 251 pages. 1941. The Macmillan Co., New York.

**WOLF CHILD AND HUMAN CHILD,** being a narrative interpretation of the life history of Kamala, the wolf girl. By Arnold Gesell, M.D., director of Yale University Clinic of Child Development. Illustrated with photographs and drawings, 107 pages. 1941, Harper and Brothers, New York.

**THE HEART IN PREGNANCY AND THE CHILDBEARING AGE.** By Burton E. Hamilton, M.D., cardiologist to the Boston Lying-in Hospital, and K. Jefferson Thomson, M.D., associate physician, Metropolitan Life Insurance Company Sanatorium, etc. With a section: Delivery and Obstetrical After-Care of Cardiacs, by Frederick C. Irving, professor of obstetrics, Harvard Medical School, etc. 402 pages. 1941, Little, Brown and Company, Boston.

**TEXTBOOK OF PEDIATRICS.** By J. P. Crozer Griffith, emeritus professor of pediatrics in the University of Pennsylvania, etc., and A. Graeue Mitchell, professor of pediatrics, College of Medicine, University of Cincinnati, etc. Third edition, revised and reset, 220 illustrations, 991 pages. 1941. W. B. Saunders Company, Philadelphia.

# ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society.** *President*, W. C. Danforth. *Secretary*, H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Next meeting, May, 1942, Sky Top, Pa.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, Frederick H. Falls, Chicago, Ill. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting will be held at the Homestead, Hot Springs, Va., September 11 to 13, 1941.
- Central Association of Obstetricians and Gynecologists.** *President*, Thomas B. Sellers, New Orleans, La. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Next meeting, New Orleans, La., Fall of 1941.
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, R. A. Bartholomew, Atlanta, Ga. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February, 1942, Atlanta, Ga.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, W. T. Dannreuther. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June, 1942, Atlantic City, N. J.
- New York Obstetrical Society.** *President*, H. J. Stander. *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, T. L. Montgomery. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Harold K. Gibson. *Secretary*, James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, George G. Cochran. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** *President*, Abraham Samuels. *Secretary-Treasurer*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Robert F. Monroe. *Secretary*, Layman A. Gray, 332 West Broadway, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, S. A. Chalfant. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** *President*, John Rock. *Secretary*, Judson A. Smith, 264 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.
- New England Obstetrical and Gynecological Society.** *President*, Frederick L. Good. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** *President*, John Vruwink. *President-Elect*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, Los Angeles, Calif., November 5 to 8, 1941.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

of discomforts to seek help, the disease is far advanced. Even when the patient is seen early, the technique for making a positive diagnosis is not simple, as it involves a biopsy followed by the procedures necessary for microscopic examination, all of which are time consuming and relatively expensive. If by any chance a simple, inexpensive method of diagnosis could be evolved which could be applied to large numbers of women in the cancer-bearing period of life, we would be in a position to discover the disease in its incipency much more frequently than is now possible. It is our purpose to present in this preliminary report the results of experimentation with such a method of diagnosis which appears to have great possibilities and which has been in use at the New York Hospital for the past eighteen months.

One of us (Papanicolaou) has studied the normal and abnormal variations in the vaginal smear in women and in animals for many years. Through these studies,<sup>2, 3</sup> which have been conducted since 1923 at the Woman's Hospital, at the New York Hospital, and at the Memorial Hospital, he has become aware of the fact that carcinoma of the fundus and carcinoma of the cervix are to some extent exfoliative lesions, in the sense that cells at the free surface of the growth tend to be dislodged and subsequently find their way into the vagina. Furthermore, a technique for collecting the cellular debris, smearing it upon glass slides, and staining it has been perfected, so that the various components may be studied. The method is so simple and inexpensive that it may be applied to large numbers of women.

#### METHOD OF TAKING THE VAGINAL SMEAR

A slightly curved glass pipette, 6 inches in length, 0.5 cm. in diameter, with a rounded tip and a small opening, and equipped with a strong rubber bulb for producing suction is used (Fig. 1). The patient is placed upon an examining table in the lithotomy position. The labia are separated and the rubber bulb compressed. The glass pipette is introduced into the posterior fornix of the vagina. The pressure on the bulb is then released and the suction produced serves to aspirate vaginal fluid with its cellular content into the glass tube. While aspiration is in progress, the tip of the tube is moved from one side of the fornix to the other so that all parts are sampled. The pipette is then withdrawn, and the vaginal material is spread upon the surface of a clean microscope slide with a sudden pressure on the bulb. Further spreading with the convex side of the pipette is advisable when the amount of fluid is abundant, as in cases where there is considerable bleeding. Very thick smears are not well penetrated by the fixing fluids and cannot be uniformly stained.

The slides are immediately plunged into a solution of equal parts of 95 per cent alcohol and ether. Drying of the smears should be carefully avoided as it results in the loss of the sharp outlines of the cells and in a change in their staining reactions. The fixation does not require more than a few minutes, but smears may be kept in the alcohol-ether solution over a long period of time and may be shipped in bottles. It is recommended that the slides not be kept in the fixative for more than a week or two as the cells slowly tend to lose their normal staining reaction. If ether is not available, plain alcohol (95 per cent) can be used. For shipping slides, a square bottle  $1\frac{3}{4}$  by  $1\frac{3}{4}$  by  $4\frac{1}{2}$  inches may be used (Fig. 1). Such a bottle may hold as many as 7 or 8 slides. An ordinary paper clip attached to each or every other one of the slides (Fig. 1) prevents the smears from rubbing against one another.

A few precautions should be observed in the procurement of material for the vaginal smear. The vaginal contents should not have been disturbed by any form of examination or treatment. Douching or bathing will, of course, dilute or com-

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AUGUST, 1941

No. 2

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## Original Communications

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### THE DIAGNOSTIC VALUE OF VAGINAL SMEARS IN CARCINOMA OF THE UTERUS\*

GEORGE N. PAPANICOLAOU, M.D., PH.D., AND HERBERT F. TRAUT, M.D.,  
NEW YORK, N. Y.

*(From the Departments of Anatomy and of Gynecology and Obstetrics of the  
Cornell University Medical College and the New York Hospital)*

THE death rate from carcinoma of the female genital tract is approximately 32,000 per year in the United States and of this figure, four-fifths, or 26,000 deaths per year, may be said to be due to cancer of the uterus. This rate has remained practically constant during the past twenty-five years.<sup>1</sup>

One of the factors probably responsible for this rather discouraging situation is the fact that, despite the progress in methods of treatment, no significant improvement has been achieved in the diagnosis of malignant growths of the female genital tract, more particularly in their early stages. Indeed, it seems very likely that until enough is known about the etiology of cancer to make it possible to place efficient prophylactic weapons in physicians' hands, no radical change in the picture can be expected unless the introduction of new methods makes possible an early diagnosis of the disease.

Early diagnosis and treatment yield a high percentage of cures in both carcinoma of the fundus and of the cervix. The present difficulty in accomplishing an early diagnosis lies in the fact that we must depend largely upon the subjective symptoms of the disease to bring the patient to the physician, and by the time the patient becomes sufficiently aware

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\*This study has been aided by the Commonwealth Fund.

Presented before the New York Obstetrical Society, March 11, 1941.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

Some nuclei are in a stage resembling prophase as if they were undergoing changes preparatory to a mitotic division. Actual mitotic figures are very rarely seen. This is probably because of the fact that the epithelial cells found in the vaginal fluid are dead desquamated cells. The nuclei are often hyperchromatic and stain intensely (Figs. 2 and 3). Others

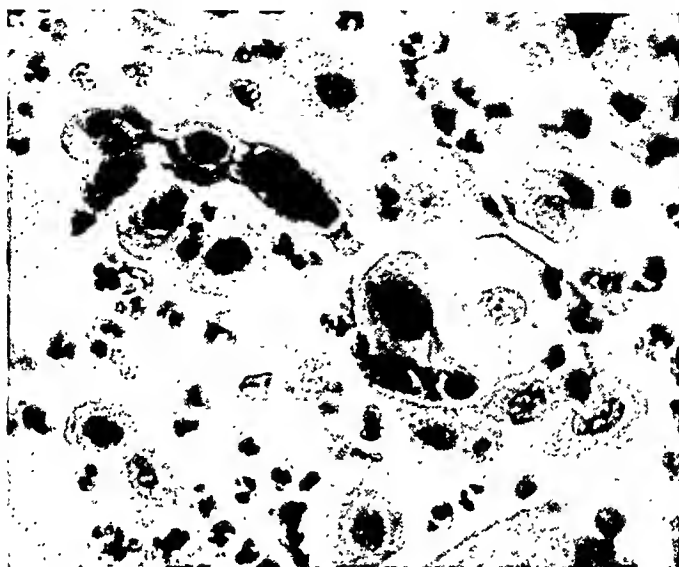


Fig. 2.—Group of normal basal cells. Menopause.  $\times 800$ .

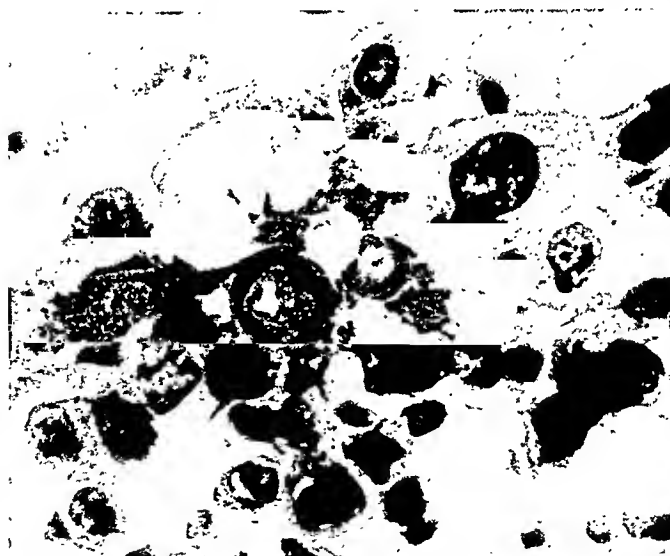


Fig. 3.—Group of abnormal cells. Carcinoma of cervix.  $\times 800$ .

become very dense and lose their fine structure, whereupon they stain very deeply (Fig. 4). Small pyknotic nuclei as well as nuclei showing various degenerative changes are frequent. Some nuclei show indentations or irregular bulging. It is not unusual to find cells with more than one nucleus (Figs. 3, 4, and 5). This is probably the result of abnormal fragmentations or of amitotic divisions.

pletely wash away the cellular deposits for a period of several hours. If there is a considerable amount of fluid of either serosal or sanguineous character, dilution will occur, in which case it is wise to make several smears to obtain the representative cell constituents which are ordinarily seen in a single smear.

#### METHOD OF STAINING VAGINAL SMEARS

Detailed instructions for staining vaginal smears are given by Papanicolaou in a recent article.<sup>4</sup> For general gynecologic diagnosis, stains DF20 or DF32 give satisfactory results. Slides are first stained in hematoxylin. A good nuclear staining is very essential for the recognition of malignant changes.

#### DESCRIPTION OF SMEARS SHOWING SQUAMOUS CARCINOMA OF THE CERVIX

Cervical malignancy, in our experience, is revealed in vaginal smears by the appearance of characteristic cells. These are, we think, derived from the superficial layers of the tumor which undergo continual desquamation. These cells show great variety of form and size, much greater

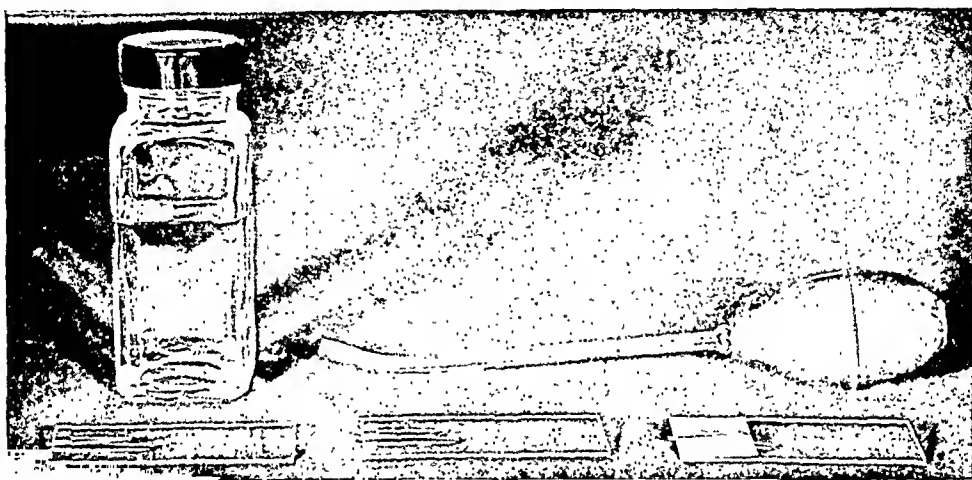


Fig. 1.—Pipette and bottle used for preparing vaginal smears.

than that seen in sections of the tumor. Their distinctive features lie in their structural abnormalities. They do not fall into the categories of any of the cell types found in the vaginal fluid of normal women or of women having benign tumors or other pathologic lesions of the uterus.

It is well to bear in mind that the isolated cells or at the most, groups of a few cells as seen in any smear preparation do not possess the orienting characteristics seen by the microscopist in tissue preparations of carcinomatous tissues, and that, therefore, a more intimate and critical knowledge of cytology is required for a correct interpretation. It is necessary, therefore, to enter into a detailed account of the characteristic appearance of the abnormal cells found in the vaginal smears of women harboring carcinoma of the fundus or cervix of the uterus.

The most characteristic feature of the abnormal cells is the atypical form and structure of their nuclei. These often are very large, far surpassing normal size (Figs. 3 and 4; compare with Fig. 2). The chromatin frequently shows a characteristic distribution in the form of conspicuous granules and of one or more small nucleoli (Figs. 3 and 4).



A commonly found, very characteristic cell type is an extremely elongated one resembling a smooth muscle fiber. Long fibrous cells of this type are modified epithelial cells and appear either isolated or in groups (Figs. 8 and 9). Another deformed cell type which is often seen is one having the form of a tadpole, with a spherical head containing

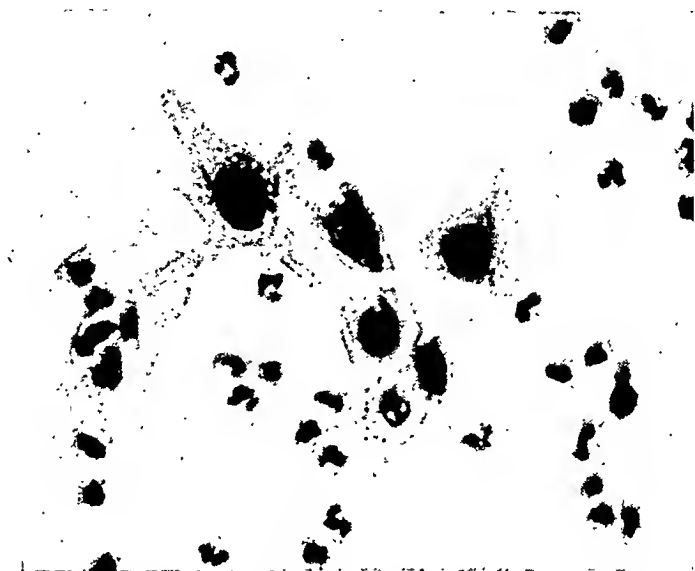


Fig. 6.—Group of aberrant basal cells. Carcinoma of cervix.  $\times 800$ .

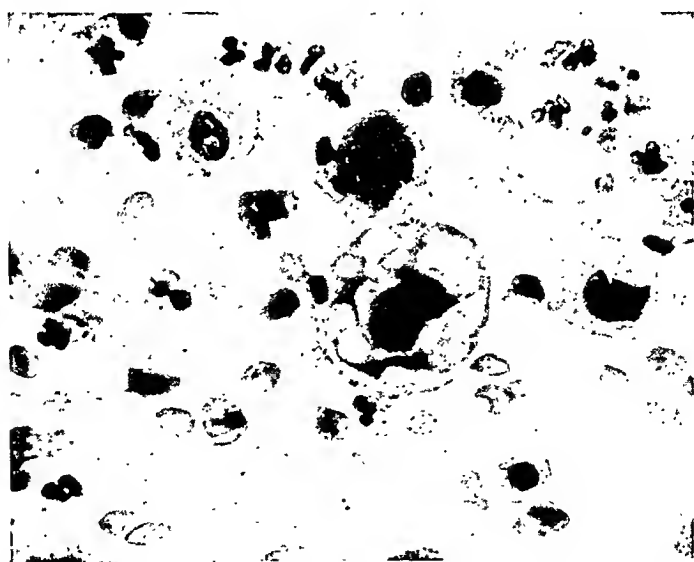


Fig. 7.—Abnormal vacuolated cell. Carcinoma of cervix.  $\times 800$ .

the nucleus and a tail-like prolongation (Fig. 9). The bulging of the heavier part which contains the nucleus is sometimes placed more centrally, causing a narrowing of the cell at both ends. Other cells attain very large sizes and acquire the most unusual forms.

The cytoplasm also shows abnormal changes. It is often dense and hyperchromatic, particularly in the cells of the basal type (Figs. 3, 4, and 5). Such cells may appear either singly or in compact dark-staining clusters. Their form and size vary greatly. Some of the basal cells assume elongate, spindlelike, triangular, or amoeboid forms (Fig. 6).

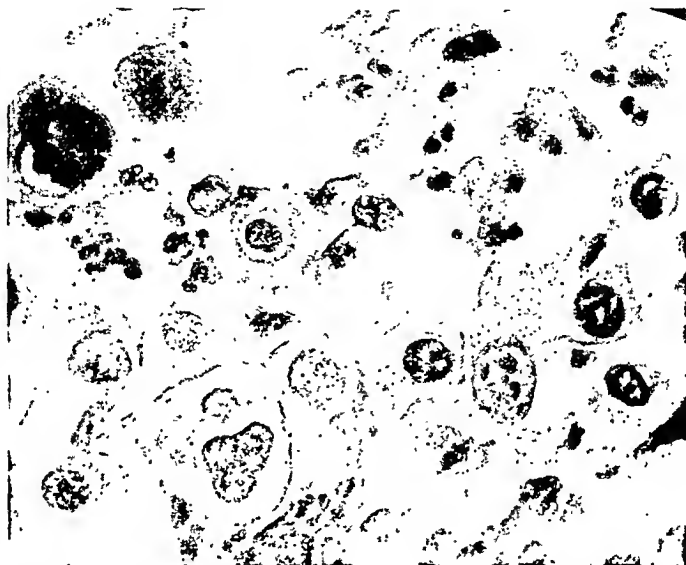


Fig. 4.—Abnormal cells. Carcinoma of cervix.  $\times 800$ .

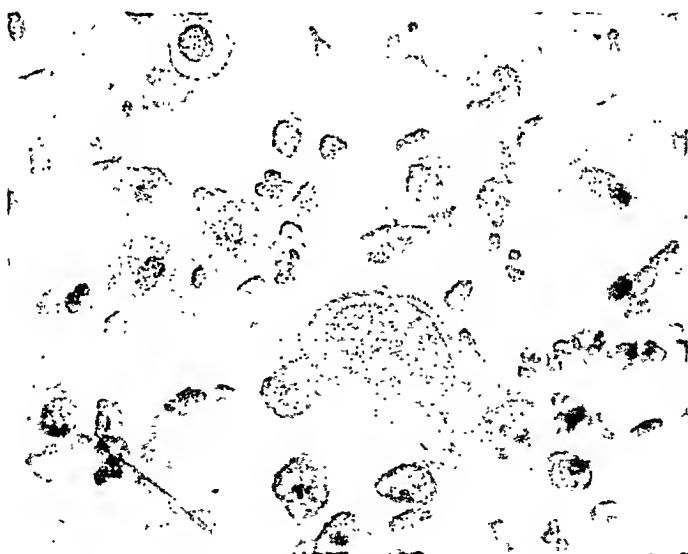


Fig. 5.—Abnormal cells. Carcinoma of cervix.  $\times 800$ .

Basal cornified cells are not uncommon. Vacuolization of the cytoplasm is a characteristic feature (Fig. 7). The vacuoles may be empty or they may contain leucocytes, erythrocytes, cellular debris, or some pink-staining fluid. Sometimes the vacuoles occupy one side of the cell, while the dense cytoplasm and the nucleus are concentrated on the other side.

bers after the menopause. The relative number of these cells varies greatly. The number and the form of the cornified cells also show considerable variability. In some cases there is an excess of cornified cells, indicating a hyperestrin condition. This was observed more frequently

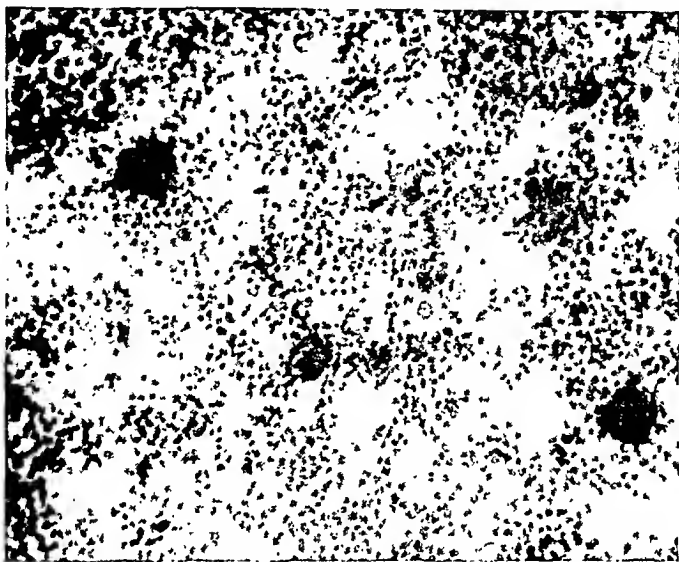


Fig. 10.—Extreme leucocytosis with clusters of polymorphonuclears. Carcinoma of cervix.  $\times 220$ .

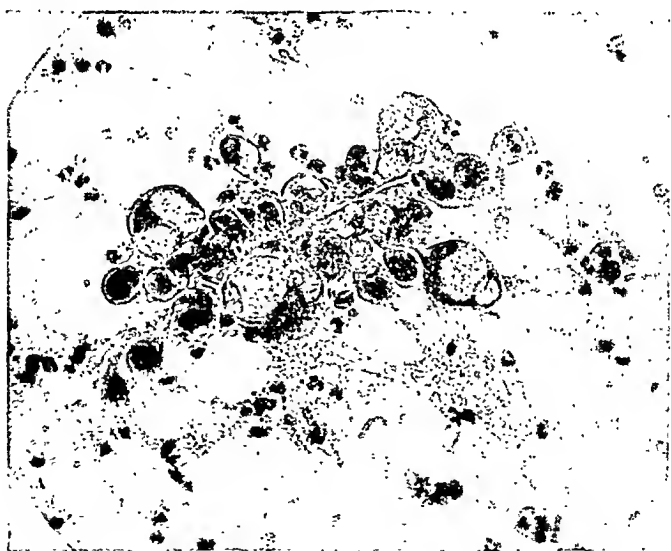


Fig. 11.—Group of abnormal histiocytes, some with very large vacuoles. Carcinoma of cervix.

in the early stages of malignancy. Cornification is sometimes due to the coexistence of other pathologic conditions like vaginitis or chronic cervicitis, or to the presence of trichomonas which is not uncommon in cases of cervical malignancy.

Blood elements are quite conspicuous in the vaginal smear of cervical malignancy. Erythrocytes are generally found in large numbers. Many

These "aberrant" cell types are numerous only in advanced cases of malignancy. They are relatively rare in the early stages of the disease and a thorough search of several slides is often necessary before their presence can be established. For this reason a negative diagnosis should always be made with extreme caution. Considering that even



Fig. 8.—Abnormal epithelial cells showing extreme elongation ("pseudofibrous" type). Carcinoma of cervix.  $\times 800$ .



Fig. 9.—"Tadpole" cell with two nuclei, and other elongated cells. Carcinoma of cervix.  $\times 800$ .

in the advanced cases the number of cells derived from the tumor forms only a small part of the total number of desquamated cells present within the vagina, it is natural to find the normal epithelial cells always in the majority. The large squamous superficial cells usually predominate in younger women, while the basal cells appear in larger num-

It is also affected by the presence of certain bacterial forms. The bacterial flora in cervical malignancies is usually rich and consists of various types with cocci and diplococci predominating. *Trichomonas* and chronic inflammatory infections may cause considerable leucocytosis.

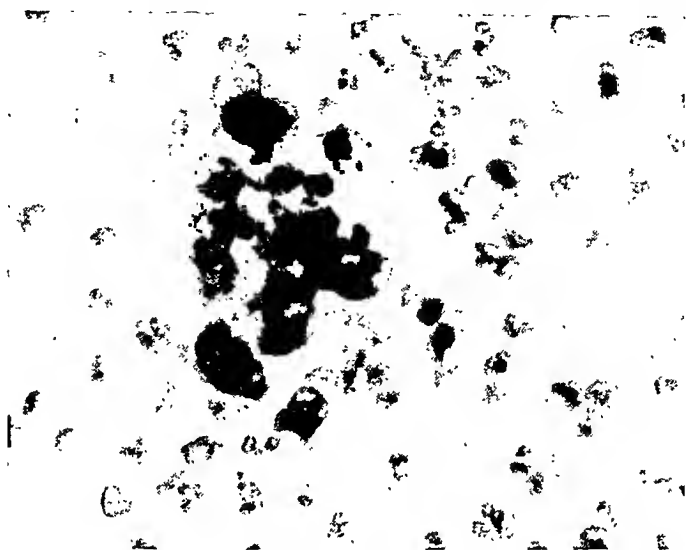


Fig. 14.—Abnormal cell group. Adenocarcinoma of fundus.  $\times 800$ .



Fig. 15.—Abnormal cell groups. Adenocarcinoma of fundus.  $\times 800$ .

The histiocytes deserve special consideration. They are invariably present in carcinoma smears and usually display a high phagocytic activity. They phagocytize dead leucocytes, erythrocytes, and other cellular debris. They appear single or in groups. Their size varies greatly. The larger ones reach the size of small epithelial cells with which they

show degeneration and have lost their hemoglobin. Fibrination is very pronounced. The complete absence of blood is so rare even in the early stages that it may be considered in favor of a negative diagnosis. The leucocytes are as a rule very numerous, more particularly in the advanced cases (Fig. 10). The polymorphonuclears are often seen in

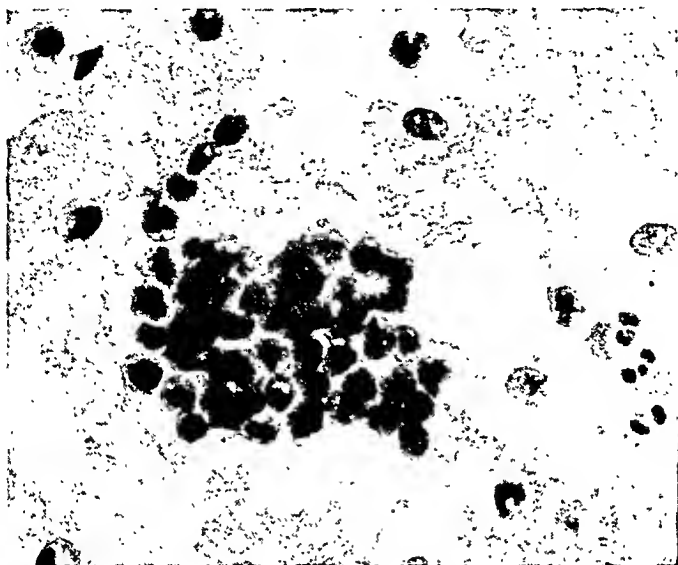


Fig. 12.—Cluster of normal endometrial cells. Menstruation.  $\times 800$ .

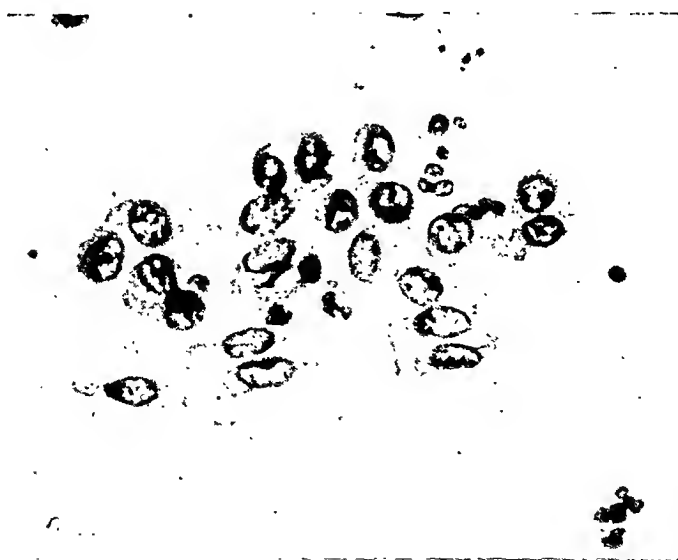


Fig. 13.—Abnormal cell group. Adenocarcinoma of fundus.  $\times 800$ .

groups which are very characteristic. Degenerating forms are not infrequent. Eosinophiles which are rarely found in normal smears are more frequently seen in malignancy, though in small numbers. Leucocytes in general have a somewhat limited diagnostic value because their number undergoes great fluctuations under different conditions.

The nuclei tend to be hyperchromatic and show marked variations in size (Figs. 14 to 17). Some are considerably enlarged (Fig. 15). They generally have an oval or rounded shape, and their chromatin is distributed in the form of conspicuous dark-staining granules. The cells are sometimes plasmolyzed and the nuclei are set free. Such nuclei appear single or in irregular clusters and are very characteristic.

The blood cells and the histiocytes show the same reactions as in carcinomas of the cervix. The histiocytes are, as a rule, numerous and display a high phagocytic activity.

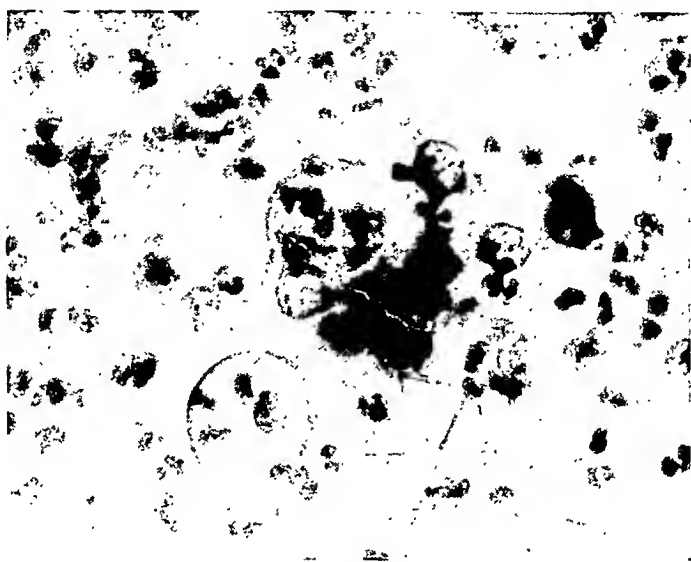


Fig. 17.—Abnormal cell group including one large histiocyte. Adenocarcinoma of fundus.  $\times 800$ .

#### SMEAR REACTIONS IN CARCINOMAS OF OTHER ORGANS OF THE FEMALE GENITAL TRACT

Carcinomas of the vagina or vulva are characterized by large, abnormal basal and superficial squamous cells, some of which are cornified. Unusually large cornified cells with highly aberrant forms and enlarged or fragmented nuclei are particularly frequent. In malignant tumors of the ovary, the findings have not been consistent. In some cases the vaginal smears showed no deviations from the normal. In others, some atypical cells have been noticed, the nature of which is somewhat obscure. It is very likely that such cells are not derived from the ovarian tumor, but from possible metastatic lesions of the uterus. The number of the cases studied up to the present is too small to permit definite conclusions.

#### DISCUSSION

It will be seen from the foregoing descriptions that the interpretation of the smear depends upon an intimate knowledge of the cytologic characteristics of the vaginal fluid. It may also be inferred that this is a somewhat more difficult matter than the problem presented by the diagnosis of carcinomatous tissues. However, it is safe to say that the

may often be confused. Their cytoplasm is vacuolated. Some of the vacuoles are large and seem to persist after digestion of engulfed elements (Fig. 11). Their nuclei tend to grow and to become hyperchromatic. Histiocytes with more than one nucleus may be seen. A good many undergo degeneration. The cytoplasm and nucleus both become pyknotic. After ingestion of erythrocytes, the cytoplasm often becomes acidophilic and stains red with eosin. The number of degenerating histiocytes appears to be relatively high.

#### DESCRIPTION OF SMEARS SHOWING ADENOCARCINOMA OF FUNDUS

The general characteristics of the vaginal smear of adenocarcinoma of the fundus are in many ways similar to those of carcinoma of the cervix. The prevailing types of "aberrant" cells are, however, of different origin. They are derived from the endometrium, and are carried

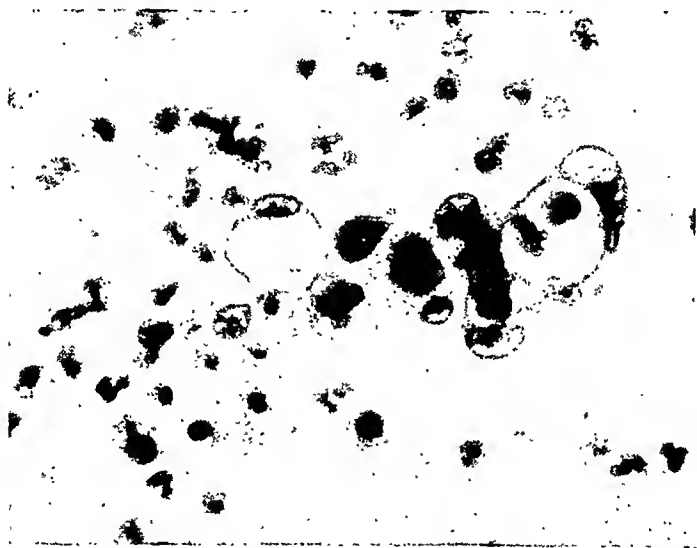


Fig. 16.—Abnormal cell group including some large histiocytes. Adenocarcinoma of fundus.  $\times 800$ .

into the vagina by the uterine bloody discharge. They do not show the high variability displayed by the modified squamous epithelial cells found in cervical carcinomas. They are considerably smaller and their variations in size and form are more limited.

The most frequently found cell types have a cuboidal, columnar, or spindle-like form and appear singly or in dark-staining clusters, which can be easily spotted with low power (Fig. 13; compare with Fig. 12). Some cells become elongated, or rounded, and show some resemblance to cells found in carcinomas of the cervix. Sometimes the cells are so densely grouped together that their outlines become very indistinct (Fig. 14). Vacuolated cells are not infrequent. A very characteristic cell type is one that has a large vacuole which is often filled with dead leucocytes or with cell debris. Such cells are evidently of histiocytic nature and perform a phagocytic action. They appear single, grouped, or intermixed with the uterine cells (Figs. 16 and 17).



DR. FRANK R. SMITH.—Any one who has seen a roentgen ray picture of a woman who has recently been curetted and then had lipiodol injected into the uterus and sees the Christmas tree effect of the dissemination of the lipiodol, would be impressed with the dangers of curettage as a method of diagnosis in carcinoma of the body of the uterus. Any method that will eliminate that obvious danger must necessarily be encouraged. At Memorial Hospital we have realized that danger for some time. We have emphasized the fact that the term curettage should be avoided, and we prefer to say that we obtain a biopsy with the curette. The advantage of having a curette or some other instrument to palpate the interior of the uterus is nevertheless not to be overlooked.

DR. HOWARD C. TAYLOR, JR.—This problem has to be met in three steps of which Dr. Traut and Dr. Papanicolaou's presentation is the first. They have succeeded in demonstrating that when certain types of cells are found, cancer is present in the cervix or the fundus of the uterus. That in itself may have considerable practical importance, because in patients in whom there is vaginal bleeding and in whom you suspect cancer of the endocervix or the corpus, you may find these cells. When the test is positive, you may almost assume that cancer is present above the external os.

The next step is the more difficult one. That is to demonstrate that when these cells are not present in the vaginal smear, cancer is not present in the cervix or the endometrium. In other words the value of negative findings in the smear must also be established from a practical standpoint which is an even more important point to establish than the first one.

The third step is to organize medical practice so that these tests may become a routine. It is worth while here to recall the experience which we have had with the Schiller test. This was a practical test, widely written about, supported by prominent gynecologists. Yet I do not think there is any gynecologic clinic which is practicing this test routinely at the present time.

DR. I. C. RUBIN.—Many years ago I had the privilege of showing several cases from the Schottländer laboratory of the von Rosthorn Clinic, Vienna, of incipient carcinoma of the cervix which were only pin point in size and were found in cases of prolapse. The diagnosis was doubted by a number of investigators. Since then the findings in the cases originally presented have been corroborated by Cullen and others, and the slides shown by Drs. Papanicolaou and Traut present the same histologic features.

The question arises as to the extent that this simple vaginal smear method will help us in diagnosing, not the obvious lesions of the cervix, but the deeply-seated carcinoma of the fundus and possibly those rare cases of Fallopian tube carcinoma from which may be shed and discarded some of these malignant cells.

The great value, besides diagnosing fundal carcinoma, is that one can avoid a traumatic curettage. A traumatic biopsy of the cervix may possibly also be avoided. If this proves diagnostic in a large number of cases of the hidden type of carcinoma and of the early, hitherto unrecognizable carcinoma of the cervix by the usual means at our disposal, including the colposcope, then we have made a great advance in the diagnostic armamentarium in this field.

requirements are not above the powers of any trained cytologist or pathologist after these have had adequate training and sufficient experience. From our experience it should be said that in general gynecologic diagnosis, the vaginal smear technique presents greater difficulties than those presented by some of the conditions in which it has been widely used, such as the evaluation of estrogenic effect upon the vaginal epithelium.<sup>5</sup>

During the past two years we have collected and studied many hundreds of vaginal smears from normal women and those suffering from gynecologic disease, and we feel that cells pathognomonic of cervical and fundal carcinoma can be definitely recognized. We are not yet in a position to offer a statistical proof of the reliability of this method of diagnosis, but we can say that in our experience it yields a high percentage of correct diagnoses when checked by tissue biopsies. There is evidence that a positive diagnosis may also be obtained in some cases of early disease. The simplicity of the method, the lack of inconvenience to the patient during its application and the possibility of obtaining daily information over a long period of time makes it very useful in following the progress of the disease after operative procedures or x-ray treatments.

In presenting this method of diagnosis at this time, we hope that it may prove to be a dependable means whereby the principal malignant diseases of the uterus can be recognized; and further that because of its simplicity, it may eventually be applied widely so that the incipient phases of the disease may come more promptly within the range of our modern modes of treatment which have been proved highly effective in early carcinoma. In conclusion, it may be well to reiterate that whereas the method makes the material for examination easily and frequently obtainable at low cost, the interpretation of the smear requires the services of a careful and discriminating cytologist who has had experience in this field. Few persons can be depended upon for this work at the present time; however, if the method proves to be worthy of further development, as we expect it to be, then it will be possible in a relatively short time to provide the necessary facilities for instruction.

#### REFERENCES

- (1) *Dublin, L. I.*: Cancer Probl., Symposium, p. 237, 1937. (2) *Papanicolaou, G. N.*: Proc. of the Third Race Betterment Conference, p. 538, 1928. (3) *Idem*: Am. J. Anat. 52: 519, 1933. (4) *Idem*: J. Lab. & Clin. Med. 26: 1200, 1941. (5) *Papanicolaou, G. N., and Shorr, E.*: AM. J. OBST. & GYN. 31: 806, 1936.

#### DISCUSSION

DR. JOSEPH HINSEY (by invitation).—This problem is one that is different from tissue pathology. In tissue pathology we have not only the cytology of the cells involved, but also the orientation of those cells in the tissues. Here we are dealing primarily with the cytology of cells and are faced with problems which are like those of the hematologist who makes his examination of the blood smear.

The interpretations presented here have been possible only through the very broad and long study which Dr. Papanicolaou has made of the cytology of these cells in the female reproductive tract, combined with the knowledge of gynecologic pathology which Dr. Traut possesses.

of the endometrium to a greater extent than that which is found. Definite proof that hyperplasia is a precursor of carcinoma has not been established.

Since uterine fibroids and endometrial carcinomas are frequent concomitant lesions (Graves, 25.7 per cent; Norris and Vogt, 26.8 per cent), and since fibroids are thought by some to be the result of estrogenic stimulation, it has been assumed by many that carcinoma of the endometrium is the direct result of estrogenic stimulation.

Such findings as these, even if they were not debatable, cannot be used as absolute proof of the etiologic importance of hyperestrinism or the unopposed action of estrin.

Experimental evidence in the rat, mouse, guinea pig, rabbit, and monkey has demonstrated several facts. Estrogens in large quantities given to these animals over prolonged periods of time have produced cystic glandular hyperplasia of the endometrium but in no instance was carcinoma produced. Carcinomatous changes were induced only when some carcinogenic agent was used in conjunction with the estrogenic therapy.

That corpora lutea are occasionally present and apparently normal in patients with endometrial carcinomas has been reported by Taylor (1932) and Herrell (1939). This leads one to conclude that it is possible for ovarian function to be normal in these patients. Definite conclusions, however, are difficult to make, since the number of premenopausal women with such malignancies is relatively small and since such patients rarely have cyclic menstruation.

#### MATERIAL

The material for this study was obtained from patients with endometrial carcinomas treated at St. Luke's Hospital, Chicago. There were 150 such patients. They were classified into two groups. In one group there were 68 patients who had been treated primarily by surgery and who had received no preoperative irradiation. The other group was composed of 82 patients who had received preoperative irradiation. The latter group was not suitable for this study, because of the possible changes in the ovaries and endometrium produced by such irradiation.

The study is concerned with the histologic and anatomic evidence of function of the ovaries and the endometria in the presence of endometrial carcinomas. It is logical, therefore, to classify the 68 patients into premenopausal and postmenopausal groups. Nineteen patients were definitely premenopausal. Forty-nine patients were in the postmenopausal group. These latter patients had no bleeding from the uterus for several years, until the onset of the bleeding associated with the carcinoma.

In each instance, the surgical and pathologic studies included accurate measurements and detailed gross and microscopic observations of both ovaries, the complete uterus, the extent of the malignant lesion, and the uninvolved endometrium. The preservation of all of the

# A STUDY OF THE OVARIES AND ENDOMETRIUMS OF PATIENTS WITH FUNDAL CARCINOMAS\*

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## INTRODUCTION

MANY theories concerning the origin of adenocarcinoma of the endometrium have been postulated. There is, however, no established proof of the direct causative factors of this malignant lesion. The theory relative to the importance of the estrogenic hormone has been based on the interpretation of concomitant ovarian and endometrial findings. The occurrence of follicular cysts, failure of ovulation, and infrequency of corpora lutea, and hyperplasia of the endometrium in patients with adenocarcinomas have been given as proof that hyperestrinism or the unopposed action of estrogen is the immediate cause of the malignancy (Taylor, 1932, 1938; Taylor and Miller, 1938; Herrell, 1939; R. Meyer, 1923; Novak and Yui, 1936; Payne, 1937; Horsley, 1924; Baecker, 1904; and Mazzola, 1938). Herrell (1939) reported the isolation of five rat units of estrin in twenty-four-hour urine specimens in 8 of 10 postmenopausal women with adenocarcinoma. Such quantities of estrin, however, are similar to those found in the urine of normal male and female castrated patients (Frank, Goldberger, and Salmon, 1936; Dingemanse, Borchardt, and Laqueur, 1937).

Taylor, in discussing the etiologic importance of estrogens, reported an instance of adenocarcinoma in association with a granulosa cell tumor of the ovary. In further support of the relationship between estrin and this type of malignancy, Herrell (1939) reported that he had not seen an endometrial carcinoma in a previously castrated patient. Baecker, Taylor, R. Meyer, and Novak and Yui have stressed the relationship between hyperplasia and endometrial carcinoma. Most authors accept the theory that hyperplasia results from unopposed estrogenic effects. Ewing (1928) reported three cases of carcinoma arising in hypertrophic glands, and Bamforth (1931) observed an early carcinoma in hyperplastic endometrium.

That the uninvolved endometrium is not unduly stimulated by the estrogens and is not hyperplastic in type in patients with carcinoma has been shown by TeLinde (1932), Fluhmann and Stephenson (1929), Hintze (1929), Healy (1937), Fluhmann (1936), Burch and others (1934), and Herrell (1939).

It is apparent that the association between hyperplasia and endometrial carcinoma is questionable. The various reports indicate that hyperplasia is not found with any great frequency in patients with carcinoma. It is logical to assume that estrogenic stimulation adequate to cause carcinoma would also stimulate the remaining portions

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three patients was not possible since the ovaries were not removed, the fact that corpora lutea were present seems well founded on the demonstration of the character of the endometrium.

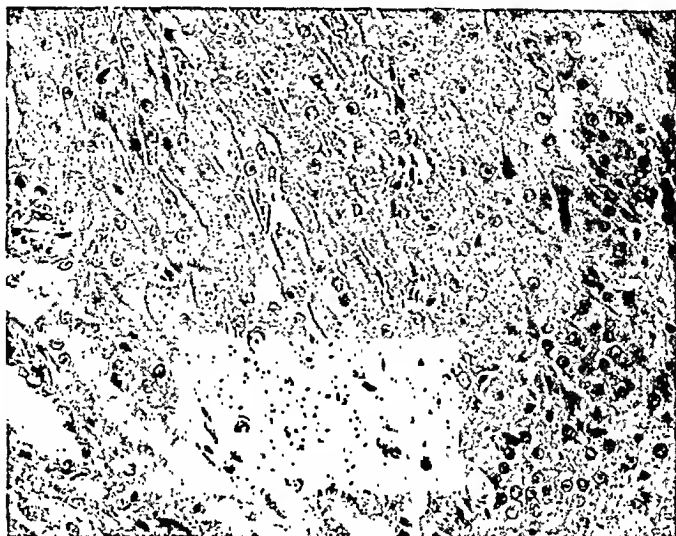


Fig. 2.—Patient L. R. The granulosa lutein cells of the histologically normal corpus luteum in an early vascularization stage are shown. This patient was operated upon on the fourteenth day of the cycle.



Fig. 3.—Patient L. R. The endometrium in an early progravid stage is consistent in degree of development with that of the corpus luteum. (See Fig. 2.)

In the 6 patients who had the ovaries removed, corpora lutea were present in five. The normal, young corpus luteum removed from Patient L. R. (Table I) on the fourteenth day had a narrow layer of fibroblasts lining the cavity. The granulosa lutein cells were large, luteinized, and contained few fat vacuoles. There was a moderate amount of connective tissue. Small vessels were also present. The theca cells were vacuolated, smaller than the granulosa lutein cells, and were grouped in the angles of the fold of the granulosa lutein layer (Fig. 2). The uninvolved endo-

paraffin blocks of the surgically removed tissues and the accurate and detailed pathologic records by Dr. Edwin F. Hirsch, Director of the Henry Baird Favill Laboratory, made this study possible.

#### PREMENOPAUSAL GROUP

The ages of the nineteen patients in this group ranged from 25 to 51 years. There were two between 25 and 29 years of age; two between 30 and 34; four between 35 and 39; six between 40 and 44; and five between 45 and 51 years of age. These patients were having menstrual bleeding in addition, in most instances, to some abnormal bleeding associated with the carcinoma. In 11 of these 19 patients exact dates of the onset and conclusion of the last menstrual periods were established. The remaining 8 patients were unable to state these dates accurately.

Two of the 11 patients who presented definite menstrual dates were operated upon on the fifth and twelfth days of the menstrual cycle, respectively. Nine patients were operated upon between the fourteenth and twenty-fifth days of the cycle (Table I).



Fig. 1.—Patient M. R. A. In this patient the endometrium removed on the eighteenth day of the cycle is progradid.

The two patients operated upon before the thirteenth day had no corpora lutea of the present menstrual cycle. The patient operated upon on the fifth day, however, had a degenerating corpus luteum of the previous cycle. If one agrees with the established fact that ovulation occurs most frequently near the midpoint of the cycle, then the absence of ovulation in these two patients is the expected finding. The portions of the endometriums not involved in the carcinomatous process in these two patients were normal postmenstrual and interval types, respectively. These findings in the endometriums and the ovaries are identical with those demonstrated in completely normal menstruating women.

In the 9 patients operated upon after the fourteenth day of the cycle, the ovaries were removed in six instances and not removed in three. The 3 patients in whom the ovaries were not removed were operated upon on the sixteenth, eighteenth, and twenty-second days of their cycles, respectively. The endometrium in each instance which was not involved in the adenocarcinoma was secretory in character (Fig. 1), indicating that corpora lutea were present and that the response of the endometrium was normal. Although demonstration of the corpora lutea in these

fixation. Only small portions of the endometrium were not involved in the malignant growth. These portions, however, were normal and typically prograavid in character.

The corpus luteum removed from Patient G. S. (Table I) on the twenty-fifth day was larger than the previous two specimens. It was normal and in the bloom stage. The granulosa lutein layer, however, was more narrow and the characteristic folds were less evident. The individual cells were large, luteinized, and contained some

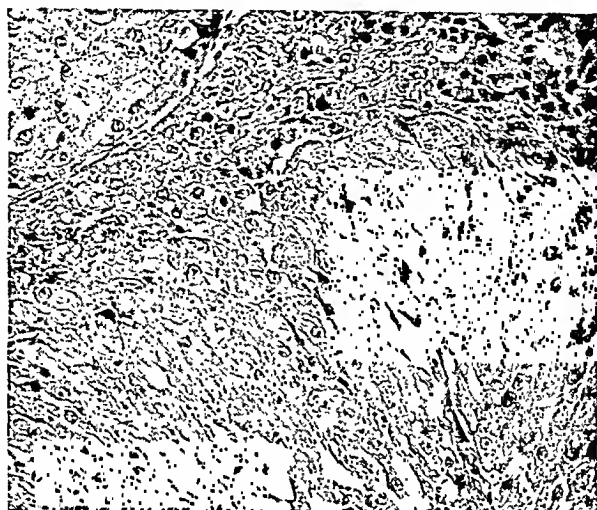


Fig. 6.—Patient L. W. The corpus luteum removed on the eighteenth day of the cycle is in the bloom stage. (See Fig. 7.)



Fig. 7.—Patient L. W. The entire endometrium was involved in the malignant change. Invasion of the myometrium which was extensive is shown.

fat vacuoles. The connective tissue lining of the central cavity was quite thick. The theca cells were scattered more or less evenly about the periphery and were highly vacuolated. The normal endometrium was late prograavid. The spiral arteries extended to the surface epithelium where branchings were numerous.

The normal, young corpus luteum removed from Patient L. W. on the eighteenth day of the menstrual cycle had a well luteinized granulosa cell layer which was markedly convoluted. Ingrown connective tissue and small vessels were not numerous (Fig. 6). A narrow layer of connective tissue lined the central cavity. There

metrium in this patient was an early, normal, pro gravid type (Fig. 3). The adenocarcinoma is shown in Fig. 4.

The corpus luteum removed from patient S. S. (Table I) on the twentieth cyclic day was in the vascularization stage and was normal. A moderately thick connective tissue layer lined the cavity (Fig. 5). Precipitated fibrin and numerous erythrocytes

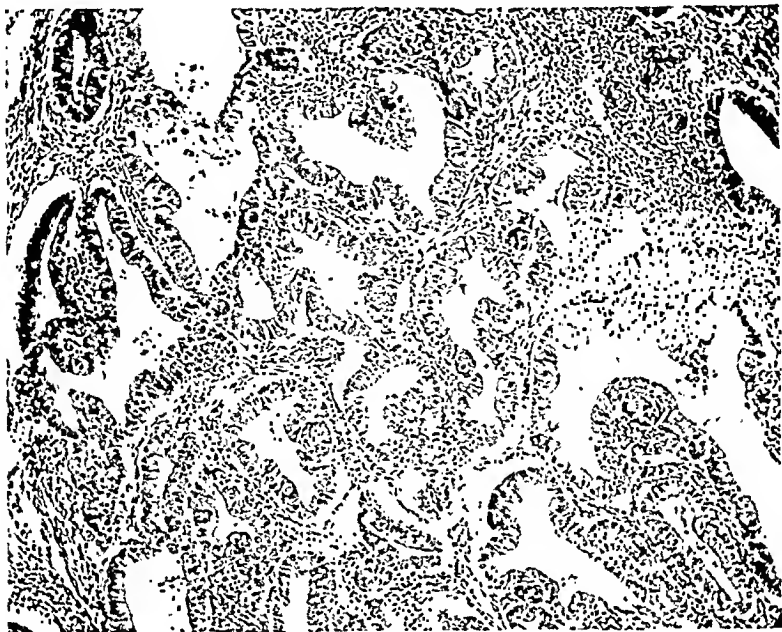


Fig. 4.—Patient L. R. The adenocarcinoma of the endometrium is shown. (See Figs. 2 and 3.)



Fig. 5.—Patient S. S. The normal corpus luteum removed on the twentieth day of the cycle is in a vascularization stage.

were intermingled with this layer. The granulosa lutein layer was thick and arranged in typical folds. The cells were large, the cytoplasm stained evenly, and there were few fat vacuoles. The theca cells were typically arranged and were well filled with vacuoles from which lipoids had been dissolved in the process of



TABLE II. PREMENSTRUAL PATIENTS

	NAME	AGE	CYCLE DATE	CORPUS LUTEUM	ENDOMETRIUM
No cyclic menstrua- tion	M. R. E.	25	?	0	Proliferative
	M. D.	29	?	0	Cystic hyperplasia
	P. F.	40	?	0	Proliferative
	M. T.	41	?	0	All carcinoma
	C. L.	41	?	0	All carcinoma
	R. S.	45	?	0	Cystic hyperplasia
	E. G.	48	?	0	Proliferative
	M. L.	45	?	?	All of tissues not available

extensive while in the other, M. D., it was only moderate. In three instances the endometrium was similar to that of a normal interval type. There was no evidence in these three of any excessive follicular hormonal stimulation. The entire endometrium in two patients was involved in the malignant process.

In the 49 patients comprising the postmenopausal group the ovaries were uniformly smaller than in the patients of the premenopausal group. There were no follicles in the great majority of instances. In only one instance was there a cyst of the ovary. The stroma of the cortex was dense. The medullar region in most contained numerous corpora albicans.

The endometrium not involved in the malignant change, in all but a few instances, was atrophic. In some patients this endometrium was more stimulated than is usual in postmenopausal patients. The ovaries in these patients, however, were atrophic and without follicles.

#### PATIENTS WITH CYSTIC OVARIES AND ENDOMETRIAL CARCINOMAS

Of the 68 patients studied here, 9 patients had cystic ovaries. Eight of these were premenopausal and one was postmenopausal (Table III). Patient M. A., aged 34 years, had in one ovary a 20 cm. pseudomucinous cystadenoma and in the other ovary a single 4 cm. follicular cyst. This patient had regular menstrual cycles and was operated upon on the fifth cyclic day. The endometrium was a normal postmenstrual type. No excessive stimulation was evident in the uninvolved portions.

Patient L. W., aged 46 years, was operated upon on the seventeenth day of her regular menstrual cycle. The ovaries were normal in size and contained three follicular cysts, the largest 1.5 cm. in diameter. A histologically normal corpus luteum was present (Fig. 6). The entire endometrium had been converted into a malignant growth.

Patient S. S., aged 30 years, had regular menstrual cycles and was operated upon on the twentieth day of the cycle. The ovaries were enlarged (Table III) and one contained four follicular cysts, 1.5 cm. in diameter, and the other ovary had a single 8.5 cm. follicular cyst. There was a histologically and functionally normal corpus luteum in the vascularization stage in one ovary (Fig. 5). The uninvolved endometrium was early pro gravid.

Patient G. S., aged 37 years, was operated upon on the twenty-fifth day of her regular menstrual cycle. The ovaries were slightly larger than normal (Table III). There were three follicular cysts, the largest 6.5 cm. in diameter. The corpus luteum was normal. The endometrium was a normal pro gravid type. As in the previous specimens, there were no excessive stimulation effects.

The follicular cysts in the ovaries of these 4 patients were not large and were not numerous. In 3 of the patients in whom some uninvolved endometrium was present, there was no evidence that these follicular cysts had produced excessive endometrial stimulation. Another fact that indicates little or no disturbance of ovarian function was the presence of normally developed corpora lutea in the three patients operated upon after the midcycle (Fig. 5). There was no functioning corpus

were few vacuoles in the granulosa lutein cells. The theca cells, containing frequent large vacuoles, were grouped in the angles of the folds of the granulosa lutein layer. The entire endometrium had undergone malignant change and had invaded the myometrium (Fig. 7).

The normal corpus luteum removed from Patient M. C., aged 51 years, on the twenty-fourth day was in the bloom stage and had a fully luteinized granulosa lutein cell layer. There was a thick connective tissue layer lining the central cavity. Many of the granulosa lutein cells contained peripherally arranged vacuoles. There was extensive vacuolization of the theca lutein cells. The endometrial carcinoma was so extensive that all the endometrium was involved. The myometrium was invaded.

TABLE I. PREMENOPAUSAL PATIENTS (19)

	NAME	AGE	CYCLE DAY OF OPERATION	CORPUS LUTEUM	ENDOMETRIUM
First half of cycle	M. A.	34	5	0	Postmenstrual
	V. C.	38	12	0	Proliferative
Second half of cycle	L. R.	42	14	+	Progravid
	R. G.	40	16	Ovary not removed	Progravid
	M. R. A.	39	18	Ovary not removed	Progravid
	L. W.	46	18	+	All carcinoma
	S. S.	30	20	+	Progravid
	J. N.	37	21	0	Proliferative
	I. C.	44	22	Ovary not removed	Progravid
	M. C.	51	24	+	All carcinoma
	G. S.	37	25	+	Progravid

The remaining patient, J. N. (Table I), was operated upon on the twenty-first day of the menstrual cycle. There was no corpus luteum present. The ovaries were 3 by 3 by 1.8 and 2.5 by 1.5 by 1 cm. in size. The ovaries contained no large follicles and no cysts. The endometrium not involved in the malignant growth was interval in type. The development was identical to that observed in the mid-cycle in the endometrium of a normal woman. This patient is the only one of this group who had not ovulated by the middle of the cycle.

The 5 corpora lutea described above are histologically normal. Their degrees of development at the time of their surgical removal are similar to that of corpora lutea removed at corresponding times from completely normal menstruating women. That three of these corpora lutea are functioning in a normal manner is evidenced by the normal and characteristic responses they have elicited in the endometria. Demonstration of the normal function of the other two corpora lutea, as determined by a study of the endometria, could not be made since the entire endometrium in both instances had undergone malignant change. In spite of the absence of any normal endometrium, the corpora lutea were normal histologically. The development of these corpora lutea was similar to that of corpora lutea removed at similar stages in the menstrual cycle from normal women. There is evidence in these two instances to indicate that endometrium is not necessary for the normal development of the corpus luteum.

The endometrium in these instances which is not involved in the carcinoma has the ability and does respond in an entirely normal manner to the follicular and corpus luteum hormonal stimulation that it receives.

So-called cystic glandular hyperplasia of the endometrium was not present in the 11 premenopausal patients who had normal cyclic menstruation.

A group of 8 premenopausal patients could not state with accuracy the dates of their last menstrual periods because of continued and profuse bleeding of various degrees (Table II). In one instance the tissues of the ovary and normal endometrium were not available for study. No corpora lutea were present in the ovaries of the remaining 7 patients.

The endometrium in two instances was characteristic of that described as cystic glandular hyperplasia (Table II). In one patient, R. S., the hyperplasia was

luteum found in the ovaries of the other patient since she was operated upon immediately postmenstrually, on the fifth day of the cycle.

That there has been no excessive estrogenic stimulation associated with the follicular cysts in these patients is indicated by: (1) The uninvolved endometrium has responded in a typical manner to normal estrogenic and corpus luteum hormone stimulation; and (2) the occurrence of ovulation and completely normal corpus luteum development and function.

The following 4 patients (Table III) are premenopausal women who had had no regular menstruation (Table III).

In patient M. R. E., aged 25 years, the ovaries were slightly enlarged and contained eight follicular cysts 1 cm. in diameter. The endometrium was proliferative in type without excessive growth. There was no corpus luteum in the ovaries.

In Patient M. D., aged 29 years, one ovary was slightly enlarged and contained three follicular cysts, 2 cm. in diameter. The other ovary was small and contained no cysts. The endometrium was characteristic of a moderate, so-called, cystic glandular hyperplasia. No corpus luteum was present.

The ovaries of Patient R. S., aged 45 years, were normal in size and contained but a single 3 cm. follicular cyst. The ovaries did not contain a corpus luteum. The endometrium evidenced marked, so-called, cystic glandular hyperplasia.

In Patient M. L., aged 45 years, the ovaries were larger than normal. In one there was a single 5 cm. follicular cyst and in the other there was a metastatic adenocarcinoma. The endometrial tissues were not available for this study.

The endometrium of two of these three premenopausal patients without cyclic menstruation evidenced the effects of either excessive or prolonged estrogenic stimulation (Table III). The cyclic ovaries found in these patients were histologically no different from those observed in the premenopausal patients with normal cyclic menstruation. The greatest degree of endometrial stimulation was noted in the patient (R. S., Table III) whose ovaries were the smallest in this group and in which there was only one small follicular cyst.

There was only 1 of 49 postmenopausal women who had cystic ovaries (Patient B. M., Table III). She was 47 years of age and had had menopausal symptoms of hot flushes and amenorrhea for only nine months. One ovary was large and contained a 10 cm. papillary cystadenoma. The other ovary was also enlarged and contained one follicular cyst 3.5 cm. in diameter. There was no corpus luteum. The endometrium evidenced slight estrogenic stimulation.

In the postmenopausal women with adenocarcinoma of the endometrium studied here, cystic ovaries were not present except in a single isolated instance. The uninvolved endometrium in these patients evidenced very little estrogenic stimulation and in many there was none.

#### SUMMARY AND CONCLUSIONS

1. Nineteen of the 68 patients studied were premenopausal. Eleven of these had cyclic menstruation. Nine of these 11 patients were operated upon between the fourteenth and twenty-fifth cyclic days. Eight possessed functioning corpora lutea. The two operated upon before the fourteenth cyclic day had corpora lutea of the previous cycle.

2. The corpora lutea were normal even in those instances in which all of the endometrium was involved in the malignant change.

3. The portion of the endometrium not involved in the malignant change in those patients with corpora lutea was normal and had responded to ovarian stimulation in a normal manner.

4. Cystic glandular hyperplasia was not present in any of the patients with cyclic menstruation.

5. Cystic glandular hyperplasia was found in 2 of the 68 patients comprising this study.

TABLE III. PATIENTS WITH OVARIAN CYSTS (9)

	NAME	AGE	CYCLE DAY	OVARIES CM.	CYSTS			CORPUS LUTEUM	ENDOMETRIUM
					NO.	SIZE	TYPE		
Premenopausal	M. A.	34	5	20 5.5 × 5 × 1.5	1	20 cm.	Pseudomucinous	0	Postmenstrual
	L. W.	46	17	4 × 3 × 1 3 × 1.5 × 1.8	1	4 cm.	Follicular	+	All carcinoma
	S. S.	30	20	8 × 6.5 × 6.5 8.5	4	1.5 cm.	Follicular	+	Progravid
	G. S.	37	25	6.5 × 4 × 3.5 7 × 5 × 4	1	6.5 cm.	Follicular	+	Progravid
	M. R. E.	25	?	5.5 × 4 × 2.5 5.5 × 3.5 × 3	2	2.4 cm.	Follicular	0	Proliferative
	M. D.	29	?	6.5 × 5 × 3 2 × 2 × 1	3	2 cm.	Follicular	0	Cystic hyperplasia
	R. S.	45	?	4 × 3.5 × 2.8 3.5 × 2 × 1	1	3 cm.	Follicular	0	Cystic hyperplasia
	M. L.	45	?	6 × 3 × 2.4 6.5 × 6 × 4	1	Metastatic adenocarcinoma 5 cm.	Follicular	1	All of tissue not available
Postmenopausal	B. M.	47		10 × 9.5 8.5 × 7 × 4	1	10 cm. 3.5 cm.	Papillary cystadenoma Follicular	0	Slight proliferative

## THECA CELL TUMORS OF THE OVARY\*

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THECA cell tumors of the ovary are mesodermal neoplasms, which reproduce the varying histologic patterns of the stroma surrounding the Graafian follicle. They also possess distinctive chemical and biologic properties. First differentiated by Loeffler and Priesel in 1932, they were designated as "fibroma theca cellulari xanthomatodes" because of their lipid content. The initial report covered 6 cases, and 4 additional theca tumors were added in 1934. Melnick and Kanter recorded the first 2 cases in American literature in 1934. Geist reported 5 cases in 1935 and added 6 others in 1938. Patterson and McCullagh, Fischer, Greenhill and Greenblatt, Collins, Varino and Weed, Ruzicka, and Traut and Marchetti also added cases of theca tumors to the rapidly accumulating literature. Dockerty of the Mayo Clinic contributed 10 cases, one with concomitant endometrial carcinoma. Eight additional theca cell tumors are herein reported, one in association with body carcinoma.

Reports of theca cell tumors stimulated early interest in their histogenesis. Geist, Gaines, and Pollack experimentally produced luteinized theca cell and granulosa cell tumors by irradiation of the ovaries of mice and concluded that genetically the theca and granulosa cells have a common origin from the parent mesenchyme of the ovary. This concept is in accord with Fisehel's recent embryologic studies. It is further supported by Corner's observation that in South American monkeys, the theca interna cell cannot be differentiated from the lutein and interstitial cell of the ovary. In 61 tumors of Graafian follicle origin (granulosa and theca cell types), Traut and Marchetti generally found an admixture of theca and granulosa cells, recording only 4 pure theca cell tumors. Novak and Gray also identified granulosa cells in theca tumors and proposed a common grouping. Though this is valid from a histogenetic and embryologic standpoint, the theca cell tumor is grossly decidedly different, from the granulosa cell type.

Theca cell tumors are unilateral, firm, solid, and vary greatly in size. In our series they ranged from 8 cm. to 25 cm. in diameter. The external surface though occasionally smooth is more often irregularly lobulated. The color varies from a gray to yellowish brown. On cut section the neoplasm may be circumscribed (Cases 6 and 7). As a rule, it is diffuse presenting a fine fibrillar pattern. Varying sized islands have a diagnostic yellow or yellow ochre color. Such zones may fuse insensibly with adjacent gray white fasciculi or are sharply circumscribed by pearly hyalinized fibrous bands which are prominent in many of the

\*Read at a meeting of the Brooklyn Gynecological Society, March 7, 1941.

6. Cystic changes in the ovaries were found in 8 premenopausal patients and in one postmenopausal patient.

7. Ovulation and corpus luteum development progressed normally, even in those patients with cystic ovaries.

8. The cystic changes in the ovaries thus were demonstrated to be incidental and without significance.

9. In patients with endometrial carcinomas, the ovaries may function normally and the uninvolved portion of the endometrium may be normal and respond normally to ovarian stimulation.

10. Thus, the etiologic significance of hyperestrinism or the unopposed action of estrin in endometrial carcinoma is not demonstrated in the patients of this report.

#### REFERENCES

- Taylor, H. C., Jr.*: AM. J. OBST. & GYNEC. 23: 309, 1932. *Idem*: Ibid. 36: 332, 1938. *Taylor, H. C., Jr., and Miller, R.*: Ibid. 36: 22, 1938. *Herrell, W. E.*: Ibid. 37: 559, 1939. *Frank, R. T., Goldberger, M. A., and Salmon, N. J.*: Proc. Soc. Exper. Biol. & Med. 33: 615, 1936. *Dingemans, E., Borchardt, H., and Laqueur, E.*: Biochem. J. 31: 500, 1937. *Meyer, R.*: Ztschr. f. Geburtsh. u. Gynäk. 85: 441, 1923. *Novak, E., and Yui, E.*: AM. J. OBST. & GYNEC. 32: 674, 1936. *Payne, F.*: Ibid. 34: 762, 1937. *Horsley, J. S.*: Ibid. 7: 106, 1924. *Baecker, J.*: Zentralbl. f. Gynäk. 28: 735, 1904. *Mazzola, V. P.*: AM. J. OBST. & GYNEC. 36: 698, 1938. *Ewing, J.*: Neoplastic Diseases, ed. 3, 1928, W. B. Saunders Co., p. 597. *Bamforth, J.*: J. Obst. & Gynaec. Brit. Emp. 38: 614, 1931. *TeLinde, R. W.*: Discussion of article by Novak, E., and Yui, E.: AM. J. OBST. & GYNEC. 32: 695, 1932. *Fluhmann, C. F., and Stephenson, H. A.*: Surg., Gynec. & Obst. 48: 425, 1929. *Hintze, O.*: Zentralbl. f. Gynäk. 53: 2396, 1929. *Healy, W.*: Discussion of paper by Payne, F.: AM. J. OBST. & GYNEC. 34: 762, 1937. *Fluhmann, C. F.*: Discussion of paper by Novak, E., and Yui, E.: AM. J. OBST. & GYNEC. 32: 696, 1936. *Burch, J. C., Phelps, D., and Wolfe, J. M.*: Arch. Path. 17: 799, 1934. *Graves, W. P.*: Gynecology, 1928, W. B. Saunders Co. *Norris, C. C., and Vogt, M. E.*: AM. J. OBST. & GYNEC. 7: 550, 1924.

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**Boisseau, Spinetta, Druelle, and Durandy:** The Infrequency of Neurosyphilis in Prostitutes, Presse méd. 47: 1658, 1939.

The writers, working in the Nice and Maritime Alps Prophylactic Medical Center, saw 1,313 cases of syphilis (287 hereditary and 1,026 acquired cases) in the period between April 1, 1938, and Feb. 15, 1939. In the group of 1,026 cases of acquired syphilis, there were 419 females. Twenty-five (6 per cent) of these women had tabes dorsalis, while in 52 other females neurosyphilis existed as cerebral syphilis (5 cases), hemiplegia (3 cases), oculopupillary disturbances (38 cases), and other nerve involvement in 6 instances.

During this same period the authors also examined 668 prostitutes, and of these 307 (46 per cent) had syphilis. None of the syphilitic prostitutes had tabes dorsalis, while in only 3 instances (1 per cent) was there evidence of oculo-pupillary involvement.

Age does not seem to explain the infrequency of neurosyphilis in prostitutes. Duration of the disease, as a factor, is difficult to evaluate although 73 of the syphilitic prostitutes were known syphilitics for nine years or more.

The writers conclude that the infrequency of neurosyphilis in a prostitute is due to the fact that such an individual receives early diagnosis and early intensive and prolonged treatment for her syphilitic disease.

CLAIR E. FOLSOME.

and Gaines, are often prominent but no constant pattern is present throughout the growth. Adjoining cells are individually separated by connective tissue fibrillae. The cell membrane is poorly defined, the cytoplasm is vacuolated and the nucleus vesicular. Ovoid cell forms simulating the granulosa cell type are inconstant. Hyaline change is frequent and the collagenous matrix supports scattered spindle and fusiform nuclei. In such areas the tumor is indistinguishable from fibromas. Calcareous deposits are not uncommon. By the silver impregnation-staining technique, demarcation of the theca cell by a pericellular fibrous reticulum is especially prominent. This technique also affords differentiation from any contained granulosa cells.

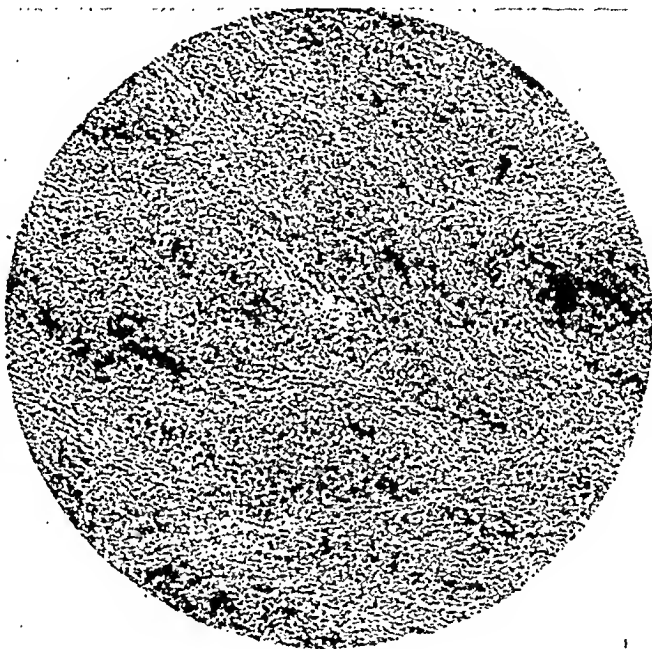


Fig. 3.—Case 1. Theca cell tumor stained by sudan III technique. The collections of dark black granules reveal accumulations of lipid globules in and between the cell bodies.  $\times 80$ .

Associated pathologic changes in the uterus are noteworthy. The endometrium often shows glandular-cystic or the more active adenomatoid hyperplasia. Occasionally epithelial proliferation is so marked that adenocarcinoma of the body is present. Of 8 cases in this series endometrium was available for study in three. Two showed glandular cystic hyperplasia (Cases 1 and 2), and focal adenocarcinoma coexisted in Case 1. The third case presented a normal premenstrual pattern. Fibromyomas of the uterus were noted in 4 of the 8 cases and adenomyosis interna in 2 of the 3 uteri available for microscopic examination.

The distinctive chemical feature of theca tumor is the content of intracellular and extracellular lipids (Fig. 3). These impart to the tumor its diffuse or more often circumscribed yellow or yellow ochre appearance so diagnostic on gross inspection. By polariscopic examination, Geist first revealed that some of these lipids are doubly refractile, indicating the presence of cholesterol or cholesterol esters. Traut more

tumors (Fig. 1). Cystic areas are not uncommonly noted and result from liquefaction necrosis (Cases 2, 3, 4, 7, and 8). In Case 4, the theca cell tumor co-existed with a simple serous cyst and could pass as adenofibroma cysticum. Microscopically, the tumor is composed of concentric, parallel or interdecussating sheaths of broad spindle, fusiform, or polygonal cells (Fig. 2). The latter called "epithelioid type," by Geist

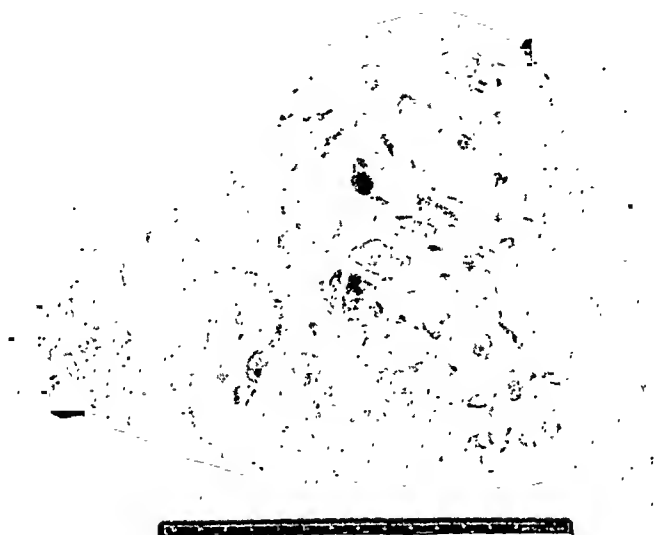


Fig. 1.—Case 2. Gross section of a theca cell tumor. Irregular yellow islands are demarcated by prominent zones of gray white hyaline. A fine reticular matrix is apparent. The numerous cysts are the result of liquefaction necrosis.

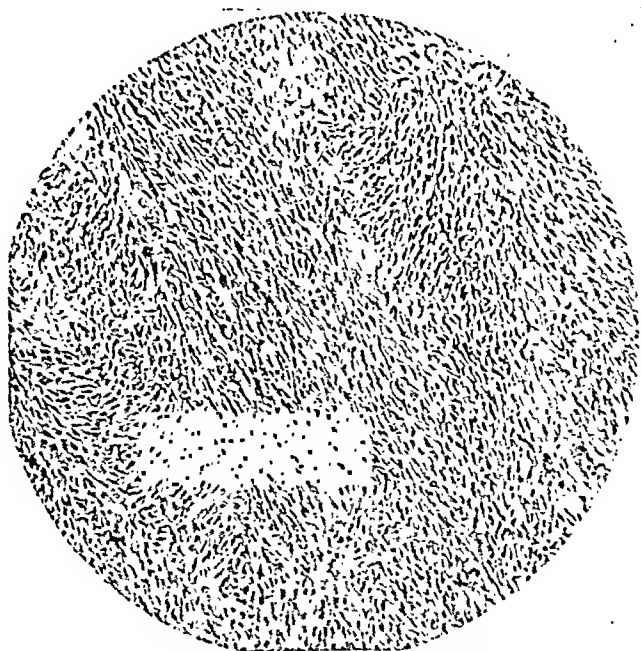


Fig. 2.—Case 2. The theca cells are arranged in broad parallel sheets, irregular whorls or interdecussating irregular angles. The pericellular reticulum is prominent. The cytoplasm is vacuolated. The vesicular nucleus is round, oval or fusiform. There are beginning collagen deposits.  $\times 200$ .



theca cell. In the primordial follicle, it is a spindle fibrous cell changing to an ovoid pseudoepithelial cell with cavitation of the maturing follicle. As shown by Aschheim it contains estrogenic hormone. After follicular rupture and the appearance of the lutein column, the theca cell shrinks, its cytoplasm becomes clear, and the nucleus pyknotic. It reverts to the inactive fibrous stromal cell in the fatty and hyaline involution phases of the corpus and no longer functions. Corner after reviewing all experiments recorded in the literature states "that estrogenic hormone is produced in the ovary and that the most probable site is the theca interna of follicles of all sizes." Allen in a more recent review on the physiology of the ovaries states, "that all ovarian tissue may secrete estrogen-granulosa, theca, interstitial and luteal, although follicular epithelium is normally the primary source."

Our own lipid studies by the differential Hoerr-Romeis staining technique indicate a relationship between high phospholipid and cholesterol content of theca tumors and menstrual anomalies which are clinical indices to hormonal aberrations. The endometrium when available gives further aid in this direction. This method, however, is not entirely accurate, for the source of hormone from any contained granulosa cells is not excluded. The ratio of phospholipid to cholesterol is decidedly varied through the tumor and is difficult to estimate adequately, unless huge numbers of blocks and sections are studied. A small tumor even if abundantly laden with lipids may not produce a total amount of hormone sufficient to evoke endometrial changes or menstrual anomalies. Hyalinized senescent tumors contain little or no lipids. In Cases 1, 3, 7, and 8), which presented menstrual anomalies, there was either diffuse or focal concentration of lipids in the sections examined. The endometrium available in Case 1 showed glandular cystic hyperplasia and focal adenocarcinoma. In Case 2, postmenopausal bleeding was lacking in spite of a glandular cystic endometrium and diffuse lipid content. Evidently this represented the amenorrheic form of hyperplasia. In Case 4, the large but markedly hyalinized tumor with scant lipid produced no menstrual aberrations. Case 5, with scant lipid content, presented menorrhagia, probably due to associated fibroids, for there were no glandular cystic changes in the endometrium. In Case 6, with only mild menorrhagia, there was abundant lipid but the tumor was small in size. The endometrium was not available for study.

The clinical features of theca cell tumors are distinctive but generally similar to those seen in granulosa cell neoplasms. They are usually encountered in women past menopausal age, although no period during active sex life is exempt. Patterson and McCullagh record a theca cell tumor in a 92-year-old woman who complained of vaginal bleeding. The removed uterus showed associated glandular cystic hyperplasia. In our series, the ages ranged from 30 to 63 years, the average was 45 years. Five were multiparas and 3 nulliparas. Menstrual anomalies comprise the most striking complaint. In women past the menopause, there is often recurrent bleeding, but it may be lacking even when glandular cystic hyperplasia is noted. In younger patients, the history is usually of menorrhagia followed by or preceded by amenorrhea or hypomenorrhea. In this series, one of three postmenopausal women experienced

recently differentiated the varied lipid components by the osmie acid-sudan III staining technique of Hoerr-Romeis. By this method the minute phospholipid globules stain faint rose pink. The somewhat large globules of free cholesterol appear yellow amber to mahogany. Cholesterol esters, neutral and acid fats appear as larger globules and stain black. This technique was followed in our series and the findings recorded in the individual pathologic reports. It must be emphasized, however, that the amount of lipids is varied in the many zones of the tumor. It is our impression that phospholipids and cholesterol are more marked where the theca cells have a fusiform or rounded appearance. Necrotic areas due to liquefaction or torsion of the tumor show large deposits of acid and neutral fat. With exceptions noted below, other ovarian neoplasms do not contain lipid. In studies of dysgerminoma, fatty acids and neutral fats were noted in areas of necrosis. In the fibrous matrix of a Brenner tumor, studied for comparison, no lipids were present. Phospholipids and cholesterol were diffusely deposited in the cell cytoplasm of three granulosa tumors. Geist and Gaines, Greenblatt, Greenhill and Brown also failed to find lipid deposits in ovarian tumors other than the granulosa cell neoplasm and arrhenoblastoma, both associated with hormonal effects.

The biologic significance of the lipids in theca cell tumors has not been entirely determined, for the function of the normal theca cell has not been fully clarified. Whether lipids are stored in the theca cells or produced in situ is unknown. Geist and Spielman have shown that theca tumors contain large quantities of estrogenic hormone. Chemically, the latter is closely related to cholesterol. It was felt, therefore, that the biologic and hormonal activity of theca tumors might be adjudged by their cholesterol and phospholipid content. An experimental basis for this concept was presented by Bloor, Okey and Corner. Their studies of corpora lutea of the sow indicate that the phospholipid content bears a direct ratio to the physiologic activity of the corpus luteum. The relation of free cholesterol to lutein activity is less clear but appears to be similar to phospholipid. Cholesterol esters appear in high ratio with retrogression of the corpus luteum. Boyd and Elden also analyzing activity of the corpora lutea of the sow conclude that the estrin content parallels the phospholipid concentration. The amount of progesterin in the corpus luteum varies inversely with the ratio of free cholesterol which is seemingly converted into hormone.

Traut, Kuder, and Cadden next employed lipid studies to determine the hormonal activity of granulosa and theca cell tumors of the human being. They used the Hoerr-Romeis staining technique and also quantitative chemical analysis for phospholipid, cholesterol, and fats. They concluded that phospholipids are indicative of hormonal potentiality and that neutral fats indicate the end stage of lipid metabolism. In a later communication, however, Traut and Marchetti indicated that pure theca cell tumors, in spite of demonstrable lipid content, may produce no appreciable hormone. They further suggested that the granulosa cells contained in theca cell tumors produced the hormone or else that theca cells produce hormones only in their early stages of growth. The latter view is more in keeping with the known cyclic changes of the

numerous and often of sinusoidal dimension. The sudan III stains showed fine globules of fat in the bodies of many of the cells as also in some of the intercellular spaces. Distribution was not uniform. Sections stained by the Hoerr-Romeis method confirmed the above. Though there was a moderate amount of phospholipid; brown cholesterol granules were predominant. There were scattered amounts of neutral and acid fat.



Fig. 4.—Case 1. Classical glandular cystic hyperplasia in association with theca cell tumor of the ovary.  $\times 80$ .

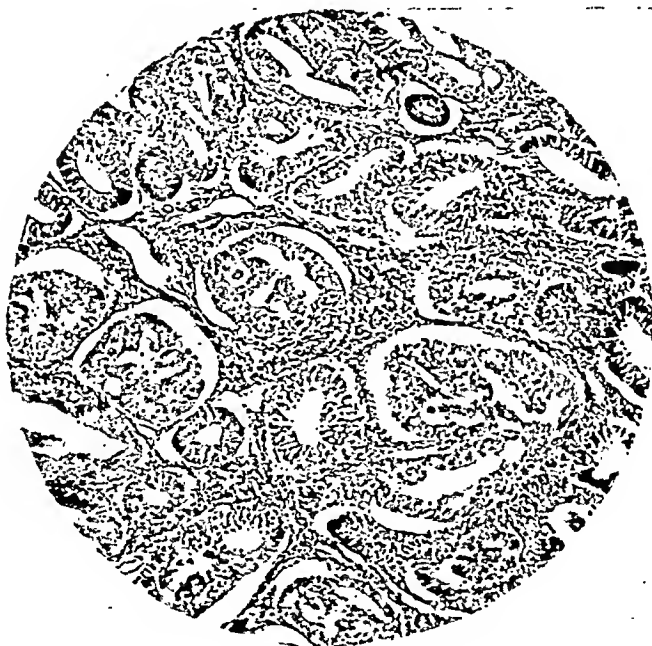


Fig. 5.—Case 1. Adenocarcinoma of the body associated with endometrial hyperplasia in theca cell tumor. Notice the irregular gland spaces, the proliferating cell buds and secondary gland spaces. Cell alignment has been lost in these more complex glands. The stroma is scant.  $\times 80$ .

vaginal bleeding (Case 1). In two 45-year-old women, oligo- and hypomenorrhea, respectively, were present (Cases 3 and 8). Of three women in active sex life, two complained of slight menorrhagia (Cases 5 and 6) and one of hypomenorrhea (Case 7). Abdominal pain was a predominant complaint in 7 of 8 cases. In four patients (Cases 3, 5, 7, and 8), this was due to complete or partial torsion of the pedicle. Physical examination generally revealed a firm, ovoid tumor mass. In 6 of 8 cases, this was noted on palpation of the abdomen. In the remaining 2, it was discovered by vaginal touch. A diagnosis of ovarian tumor, however, was made preoperatively only in 3 cases, the remaining 5 were interpreted as fibromyomas. It must be explained, however, that in 3 of these patients the theca cell tumor was associated with fibromyomas of the uterus. Theca cell tumors are usually benign, but the true incidence of malignancy remains to be established. A malignant theca tumor associated with ascites and metastasis has been reported by Loeffler and Priesel. Another malignant theca tumor with ascites was presented by Geist and Gaines. In this report all 8 theca tumors were benign although one was associated with adenocarcinoma of the body. Therapy consists in operative removal of the neoplasm.

#### CASE REPORTS

CASE 1.—Mrs. J. R. (No. 30846), aged 57 years, white, married, gravida 0, was admitted to the Long Island College Hospital on Aug. 8, 1936, complaining of leucorrhea and vaginal bleeding. Menses began at 13½ years, recurred every twenty-eight to thirty-nine days, and lasted four days. Since October, 1933, however, the periods have been very irregular, appearing at two- to twelve-month intervals. On May 14, 1936, the patient noted yellow or sanguineous vaginal discharge which had persisted until admission. The pertinent physical finding was an irregular nodular uterine mass approximating the size of a fourteen to sixteen weeks' gestation. A diagnosis of uterine fibroid and adenocarcinoma of the fundus was made. At operation there was a small quantity of clear serous fluid in the peritoneal cavity. Panhysterectomy and bilateral salpingo-oophorectomy were performed. The post-operative course was uneventful.

*Pathologic Report.*—The uterus, removed by panhysterectomy, measured 12 cm. in length, 12 cm. transversely and 7 cm. in the anteroposterior diameter. Enlargement resulted from numerous interstitial fibromyomas, the largest of which in the right cornual region measured 5 cm. in diameter. The cervix was essentially negative. The endometrium was thickened and several fundal polyps were present. The myometrium contained numerous minute fibromyomas. Microscopically, the endometrium presented classical glandular cystic hyperplasia (Fig. 4). In several areas, however, the hypertrophied glands contained proliferating cell buds which fused, resulting in formation of secondary gland spaces (Fig. 5). In such areas cell alignment had been lost. The cytoplasm was reduced in amount and the nuclei varied slightly in size, shape, and staining character. Mitotic figures were common. The stroma was compact and cellular. The myometrium was free from malignant deposits. The fibroids presented the usual appearance. The right and left tubes showed no gross or microscopic anomalies. The left ovary was atrophic.

The right ovary was converted into a firm, lobular mass which measured 13 by 8 by 6 cm. Gross section revealed a fibrillar gray white structure of irregular pattern. Circumscribed islands presented a yellow tint. Microscopically, the tumor was comprised of proliferating broad spindle cells. Deposition of intercellular hyaline was focally pronounced, and calcareous deposits occasionally encountered. Where cellularity was most marked, the spindle cells coursed in irregular sheaths which interdecussated at irregular angles. Broader fusiform cells were frequent. The cell membranes were often indistinct. The nuclei, spindle, oval, or fusiform in shape, were vesicular in character. Nucleoli were prominent. The capillaries were

TABLE II. THECA CELL TUMOR. PATHOLOGIC FINDINGS

CASE	UTERUS	OVARY				SILVER STAIN
		GROSS	MICROSCOPIC	SUDAN III	HOERR-ROMEIS	
2	Multiple fibroids. Glandular cystic hyperplasia. Endometrial polyps. Adenomyosis interna	25 × 20 × 12 cm., wt. 2,612 gm. Firm, circumscribed yellow zones, focal liquefaction necrosis	Large spindle-shaped cells. Marked intercellular hyaline	Intra- and extracellular lipid generally scant but uniform, focal concentrations present	Phospholipid pre- dominant. Cholesterol moderate. Neutral fat, scant	Broad collagenous bands, focally a fine honeycomb net- work
3		13 × 10 × 7.5 cm., wt. 554 gm. Firm, yellow gray, islands of yellow tissue	Plump spindle-shaped cells separated by bands of collagen tissue	Intracellular lipid generally scant but uniform, occasional focal concentra- tions	Phospholipid and cholesterol in equal amounts. Neutral fat, scant	Fine reticulum, occa- sional broad col- lagenous strands
4		18 × 15 × 12 cm., wt. 1,350 gm. Firm, gray white, prominent blood vessels on surface, several cystic cavities	Interdecussating sheaths of spindle cells, with inter- cellular hyaline. Also adenofibroma cysticum	Lipid scant, focal concentrations in cellular areas	Phospholipid, moder- ate. Cholesterol, predom- inant. Neutral fat, scant	
5	Multiple fibroids. Adenomyosis in- terna. Premenstrual endo- metrium	12 × 8 × 6 cm. Firm, gray white, islands of yellow tissue	Collagen prominent. Occasional cellular areas of spindle cells	Lipids scant, clustered in small areas	Phospholipid, scant. Cholesterol, predomi- nant. Neutral fat, rare	Fine pericellular re- ticulum

TABLE I. THECA CELL TUMOR. CLINICAL FINDINGS

CASE	AGE AND GRAVIDITY	MENTES	CHIEF COMPLAINT	FINDINGS	PREOPERATIVE DIAGNOSIS	OPERATIVE FINDINGS	OPERATION
2	G. A., 53 Para i	Menopause, 2 yr. No bleeding to date	Enlargement of abdomen, abd. pain, urinary frequency 2 mo.	Irreg. suprapubic mass, size of 5 mo. pregnancy	Fibromyoma of uterus	Fibromyoma of uterus, tumor of left ovary	Supracervical hysterectomy. Left salpingo-oophorectomy
3	M. V., 45 Para vi	14 x 28-35 x 3. In last yr., flow lasts only 1-2 days	Lower abd. pain, nausea constipation 4 days	Supra pubic mass extending to umbilicus. Uterus small, crowded to right	Solid rt. ovarian neoplasm with torsion	4 ounces of free fluid. Torsion of solid rt. ovarian tumor	Rt. salpingo-oophorectomy
4	S. C., 63 Para v	Menopause, 16 yr. No bleeding to date	Lower abd. pain, urinary frequency 1 mo.	Suprapubic mass extending to umbilicus	Fibromyomas of uterus	6 ounces of free fluid. Uterus small, solid left ovarian tumor	Left salpingo-oophorectomy
5	H. D., 38 Grav. 0	12 x 28 x 5, mod. profuse	Severe lower abd. pain, nausea 1 day	Uterus, irregular, size of 4 mo. preg. Mass in cul-de-sac	Fibromyomas of uterus with degeneration	Fibromyoma of uterus, solid rt. ovarian tumor with torsion	Supracervical hysterectomy, bilat. salpingo-oophorectomy
6	F. B., 31 Para ii	12 x 25-28 x 5-6	Pain in R.L.Q., backache 10 days	Uterus normal, firm mass in rt. fornix	Solid rt. ovarian tumor	100 c.c. straw-colored fluid, uterus small, fibroid nodule on ant. wall. Solid tumor of rt. ovary with torsion	Rt. salpingo-oophorectomy. Myomectomy
7	H. F., 30 Para i	13 x 28 x 3. In last yr., flow only 15 hr., scant, muddy	Pain in R.L.Q., 1 yr.	Uterus normal. Mass, size of orange, in rt. fornix	Rt. ovarian cystoma	Uterus and left adnexa normal. Rt. ovarian tumor with partial twist	Rt. salpingo-oophorectomy
8	S. H., 45 Grav. 0	Scant and irreg. menses for several mo., previously regular	Pain in L.L.Q. 1 day	Suprapubic mass extending 2 fingers above umbilicus	Fibromyoma of uterus	Straw-colored fluid in peritoneal cavity. Uterus and rt. adnexa normal, left ovarian tumor with torsion	Left oophorectomy

Diagnosis: Endometrial hyperplasia; focal adenocarcinoma, multiple fibromyomas (interstitial), and theca cell tumor of right ovary.

The clinical history, physical and pathologic findings of the remaining 7 cases are abstracted in Tables I and II.

### CONCLUSIONS

1. Theca cell tumors arise from the mesenchyme of the ovary and histogenetically are related to granulosa cell neoplasms.

2. A diffuse or more often insular yellow appearance on cut section is distinctive and allows gross differentiation from ovarian fibroma which it otherwise so closely resembles.

3. Microscopically, the tumor is composed of concentric, parallel or interdecussating sheaths of broad spindle, fusiform or polygonal cells each surrounded by fine connective tissue fibrillas. The Foote or Laidlaw silver stains afford easy demonstration of pericellular network.

4. The microscopic demonstration of intracellular lipids is distinctive. Free cholesterol, cholesterol esters, phospholipids, acid, and neutral fats are recognizable by the Hoerr-Romeis staining technique.

5. The quantitative ratios of the varied lipid fractions studied in conjunction with the endometrial pattern afford some index to the biologic activity of the tumor.

6. Eight cases of theca cell tumors are reviewed. Associated uterine pathology is frequent. Glandular cystic hyperplasia, one with adenocarcinoma was present in two of three uteri available for study. Fibromyomas occurred in one-half of the cases.

7. Amenorrhea or atypical menstrual bleeding is the predominant complaint. Pain, if present, is due to torsion or rotation of the tumor.

8. The presence of a unilateral solid pelvic tumor, independent of the uterus and associated with postmenopausal bleeding or menstrual irregularities, is suggestive of a theca cell tumor of the ovary. Granulosa cell neoplasms, however, must be excluded.

Our thanks are hereby extended to Dr. Max Lederer, Director of Laboratories of the Jewish Hospital, for permission to review the pathologic material, and to Drs. L. S. Schwartz, T. S. Welton, I. Tran, and S. Livingston for permission to review their cases.

### REFERENCES

- (1) Allen, Edgar: J. A. M. A. 116: 405, 1941. (2) Bloor, W. R., Okey, R., and Corner, G. W.: J. Biol. Chem. 86: 291, 1930. (3) Boyd, E. M., and Elden, C. A.: Endocrinology 19: 599, 1935. (4) Collins, C. G., Varino, G., and Weed, J. C.: J. A. M. A. 113: 1634, 1939. (5) Corner, G. W.: Physiol. Rev. 18: 154, 1938. (6) Dockerty, M. B.: AM. J. OBST. & GYNEC. 39: 434, 1940. (7) Fischer, H. S.: Ibid. 35: 1070, 1938. (8) Furth, J., and Butterworth, J. S.: Am. J. Cancer 28: 66, 1936. (9) Geist, S. H., and Spielman, F.: J. A. M. A. 104: 2173, 1935. (10) Geist, S. H.: AM. J. OBST. & GYNEC. 30: 480, 1935. (11) Idem: Ibid. 30: 650, 1935. (12) Geist, S. H., and Gaines, J. A.: Ibid. 35: 39, 1938. (13) Geist, S. H., Gaines, J. A., and Pollack, A. D.: Ibid. 38: 786, 1939. (14) Greenblatt, R. B., Greenhill, J. P., and Brown, W. R.: Ibid. 37: 929, 1939. (15) Idem: Ibid. 36: 684, 1939. (16) Kellert, Ellis: Arch. Path. 17: 602, 1934. (17) Loeffler, E., and Priesel, A.: Beitr. z. path. anat. u. z. allg. Path. 90: 199, 1932. (18) Idem: Wien. med. Wehnschr. 84: 400, 1934. (19) Melnick, P. J., and Kanter, A. E.: AM. J. OBST. & GYNEC. 27: 41, 1934. (20) Meyer, R.: Ibid. 22: 697, 1931. (21) Novak, E., and Gray, L. A.: Ibid. 31: 213, 1936. (22) Patterson and McCullagh: J. Obst. & Gynaec. Brit. Emp. 43: 1186, 1936. (23) Ruzicka, J.: Arch. f. Gynäk. 169: 601, 1939. (24) Traut, H. F., and Butterworth, J. S.: AM. J. OBST. & GYNEC. 34: 987, 1937. (25) Traut, N. F., Kuder, A., and Cadden, J. F.: Ibid. 38: 798, 1939. (26) Traut, H. F., and Marchetti, A. A.: Surg. Gynec. & Obst. 70: 632, 1940.

6	Solitary myoma	8 x 8.5 x 4 cm. Firm, gray white, fibrillar pattern, irregular mottling due to circulatory change. Tumor circumscribed	Areas of edema and interstitial hemorrhage. Sheaths of cells surrounded by fine reticulum. Hyaline in acellular areas	Diffuse lipids	Phospholipid and cholesterol, numerous. Neutral fat, scant	Fine pericellular reticulum
7		9 x 8 x 3.5 cm. Firm, gray white, reticulated appearance many cystic cavities due to liquefaction necrosis	Interdecussating sheaths of spindle and fusiform cells, separated by connective tissue septa	Focal concentrations of lipid	Phospholipid and cholesterol equal in cellular zones. No neutral fat	Fine reticulum in cellular areas. Broad zones of wavy collagen in acellular areas
8		22 x 17 x 10 cm. Solid segment is gray white, reticulated. Lower cystic segment	Sheaths of cells, interdecussating or arranged in concentric whorls, embedded in hyaline matrix. Edema focally present	Uniform distribution of intracellular lipid	Scant but uniform phospholipid and cholesterol. Neutral fat, scant	



Presumably these renal vascular changes are caused by, or concomitantly with the toxemia. Do they persist?

Bell described old glomerular lesions in a woman dying of recurrent eclampsia seven years after the original attack. He considered that such lesions do persist, and that the posttoxic hypertension, so often found, might be explicable on this basis. Baird and Dunn did not find the same lesion persisting eighteen months after eclampsia, in the one case which they examined after an interval. Page and Cox<sup>14</sup> have added observations on 7 more patients dying of various causes at different times after toxemia of pregnancy. In all cases they found some degree of thickening in the glomerular basement membranes, which they believed to have persisted as a sequela of toxemia. Kellar, Arnott and Matthew<sup>15</sup> did not examine any cases surviving the acute toxemia, but thought that it is "not unreasonable to suppose that in a certain number of cases the lesion will progress and develop into a fully established chronic nephritis." However, Kellar<sup>16</sup> later failed to find such changes in the kidneys of 3 women dying of recurrent toxemia.

Since the glomerular lesions might gradually heal, even in the presence of hypertension, the ideal material for pathologic study would be the kidneys of women dying accidentally a few months or a very few years after the toxemia of pregnancy. As we have seen, such observations are very few, and these are contradictory. We have, therefore, attempted an *in vivo* "chemical dissection" of the kidney in a series of posttoxic women. These observations on the renal and glomerular hemodynamics may be interpreted as supporting the hypothesis that toxemia of pregnancy does leave renal-vascular damage. Perhaps this damage may initiate the vicious cycle causing hypertension.

#### METHOD

Smith, Goldring, and Chasis<sup>17</sup> have found that, at low plasma concentrations, diodrast has a renal extraction ratio of very nearly 100 per cent. That is, however much goes in the renal artery none comes out the renal vein, because all the diodrast is removed (and excreted) on one perfusion of the kidney. Measurement of the blood level of diodrast and of the quantity excreted each minute, then, enables one to calculate the volume of plasma (or whole blood) which must have perfused the kidney to provide the diodrast excreted.

The volume of glomerular filtration may be measured simultaneously by determination of the ratio of the quantity of inulin excreted each minute to the plasma level of inulin, since inulin is neither excreted nor reabsorbed by the renal tubule cells (Smith<sup>18</sup>). Also, the volume of filtrate may be approximated from the maximal urea clearance. Usually the maximal urea clearance, in milliliters per minute, is about 60 per cent of the glomerular filtration.

Simultaneous measurement of the plasma flow (diodrast clearance) and glomerular filtration (inulin clearance or  $\frac{\text{urea clearance}}{0.60}$ ) permits us to calculate what pro-

portion of plasma is filtered into Bowman's capsule as "pre-urine." This is a most useful calculation, and the quotient of  $\frac{\text{glomerular filtration}}{\text{plasma flow}}$  is called the "filtration fraction."

#### RESULTS AND DISCUSSION

In Table I are summarized the observations made in 30 normal women, and in 11 hypertensive women who have never had a toxic pregnancy. Normally the filtration averages about 116 ml. per minute, the renal plasma flow averages 567 ml. per minute, and the filtration

## THE QUESTION OF GLOMERULAR DAMAGE FOLLOWING TOXEMIA OF PREGNANCY

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MANY posttoxic women eventually develop hypertension, and we have found that the status at fifty-two months (average) post partum is very definitely correlated with factors which suggest that toxemia causes damage which is associated with the finding of hypertension at this time. (These factors are, particularly, the duration of toxemia and repeated toxemias, Chesley and Somers,<sup>1</sup> Chesley and others<sup>2</sup>.) Perhaps these women with high blood pressure at fifty-two months post partum merely have hypertension earlier than they otherwise might. We do believe that some degree of control over the appearance of hypertension after toxemia is possible, but we cannot say whether this control is postponement or prevention.

In seeking the answer to the question of whether toxemia of pregnancy causes vascular-renal damage, one first looks to pathologico-anatomic observations. There are several reports in the literature describing renal changes as found at autopsy some years after the toxic pregnancy (Heynemann,<sup>3</sup> Herrick and Tillman,<sup>4</sup> McKelvey and MacMahon,<sup>5</sup> Zimmerman and Peters<sup>6</sup>). In nearly all of these cases the patients have died of cardiovascular-renal disease after a more or less prolonged course of hypertension. The pathologic findings have usually been those of nephrosclerosis secondary to the hypertensive cardiovascular disease. The significance of these studies is that they establish the usual nature of the posttoxic hypertension which has been so often miscalled "chronic nephritis." In some cases either true chronic glomerulonephritis or pyelonephritis has been found; these diseases, when found, frequently having antedated the toxic pregnancy. Herrick, Tillman, and Grebene<sup>7</sup> in 1936 wrote: "To confuse this disease (hypertensive cardiovascular disease—L.C.C.) with nephritis is to be blind to a well and long accepted opinion of the medical clinic and of the pathologic laboratory." Since 1936 Page<sup>8</sup> has adduced strong evidence that there may be a causative renal factor for the high blood pressure found in many cases of hypertensive cardiovascular disease ("essential" or "primary" hypertension). Even though this be true, it seems worth while to differentiate between this disease and chronic nephritis.

The anatomic studies just cited do not answer the question as to what changes, if any, are specifically caused and left by the toxemia of pregnancy.

Glomerular lesions in the acute phase of eclampsia have been described by Löhlein,<sup>9</sup> Fahr,<sup>10</sup> Lubarsch,<sup>11</sup> Bell,<sup>12</sup> Baird and Dunn,<sup>13</sup> and by several others. The typical lesion seems to be a thickening of the basement membrane of the glomerular capillaries, often with an increase in thickness and occasionally in number of endothelial cells. The significant result of these changes is that the lumina of the glomerular capillaries are narrowed.

We have measured the renal plasma flow in 15 women with hypertension following toxemia of pregnancy, and in 7 posttoxemic women with normal blood pressures. Simultaneously we have determined the urea clearances, and made a rough estimate of the glomerular filtration therefrom. The data in Table II indicate that the filtration fraction is normal in all but 2 cases, though considerable decreases are usually found in the renal plasma flows. This is in marked contrast to the findings in the "male type" of hypertension.

In posttoxemic hypertension, we find: (a) diminished plasma flow (usually), (b) diminished filtration (usually), and (c) normal filtration fraction. These findings point to the glomerular capillaries as the site of obstruction to the blood flow. Either there are fewer glomeruli than normal, or the lumina of the capillaries are narrowed. It is just such capillary narrowing which Bell,<sup>12</sup> and Page and Cox<sup>14</sup> have described as persisting after toxemia of pregnancy. If these glomerular

TABLE II. RENAL HEMODYNAMICS IN POSTTOXEMIC HYPERTENSIVE WOMEN

AGE YEARS	POST PARTUM YEARS	BLOOD PRESSURE MM. HG	PLASMA CLEARANCE OF		CALCULATED GLOMERULAR FILTRATION ML. PER MINUTE	FILTRA- TION FRACTION PER CENT	DEFICIT IN RENAL BLOOD FLOW* PER CENT
			DIO- DRAST ML. PER MINUTE	UREA ML. PER MINUTE			
41	0.1	170/106	358	68.0	113.3	31.6	41
30	1.3	192/120	434	48.1	80.1	18.5	18
34	3.2	152/90	403	52.0	86.7	21.5	30
37	3.4	180/130	538	58.4	97.3	18.1	2
48	4.7	168/90	430	43.2	72.0	16.8	10
37	2.2	170/120	437	70.2	116.9	26.8	17
48	3.6	150/90	517	62.2	103.6	20.0	4
38	5.5	210/140	376	38.3	63.8	17.0	33
40	2.0	240/126	450	57.9	96.5	21.5	24
39	1.8	220/120	377	40.5	67.5	17.9	30
48	5.0	220/110	382	38.6	64.4	16.8	31
40	4.0	190/150	349	47.5	79.2	22.7	40
30	0.6	180/120	454	53.2	88.8	19.5	19
24	0.1	170/100	531	63.0	105.0	19.8	10
35	1.3	140/90	392	54.9	91.6	23.3	28

\*As compared with average normal of 850 ml. per minute.

lesions do persist, they serve to explain the renal blood flows and filtration fractions which we have observed. Since the thickening of the basement membranes of the glomerular capillaries is thought to be specific for toxemia of pregnancy, it would follow that the renal ischemia found at follow-up is a consequence of the toxemia.

There are two possible alternative explanations for the observed relationships between the plasma flows and filtration volumes. (a) Both afferent and efferent arterioles may be constricted, the increased tonus being so balanced as to maintain a normal filtration fraction at the expense of the filtration volume. (b) Since the glomerular filtration is estimated from the maximal urea clearance, an unusually great back-diffusion of urea from the tubules could account for an *apparent* reduction in filtration volume. This increased back-diffusion of urea would then have to be exactly balanced with the renal blood flow so as to main-

fraction is about 20 per cent. In the hypertensive women who have had no pregnancies or no toxemias of pregnancy, the renal blood flow is characteristically reduced while the filtration remains relatively normal because of the high filtration fraction. These changes have been described as typical for essential hypertension in men, and to avoid circumlocution we shall refer to these patients as having the "male type" of hypertension.

TABLE I. SUMMARY OF OBSERVATIONS ON RENAL HEMODYNAMICS IN NORMAL WOMEN, AND IN HYPERTENSIVE WOMEN WHO HAVE NEVER HAD A TOXEMIA OF PREGNANCY. COMPLETE DATA FOR EACH CASE HAVE BEEN PUBLISHED ELSEWHERE (CHESLEY AND CHESLEY<sup>19</sup>)

CASES	MEAN AND RANGE	GLOMERULAR FILTRATION ML./MIN.	PLASMA FLOW ML./MIN.	FILTRATION FRACTION PER CENT	RENAL BLOOD FLOW ML./MIN.	DEFICIT IN BLOOD FLOW PER CENT
<i>Normal Women</i>						
30	Mean	116	567	20.4	850	0
	High	163	848	24.5	1233	
	Low	75	459	15.2	693	18
<i>"Male Type" Essential Hypertension</i>						
11	Mean	106	351	30.2	559	34
	High	128	557	45.4	685*	19*
	Low	32	96	25.0*	153	82

\*Excluding 3 cases with normal renal blood flow; lowest filtration fraction of these 3 is 21.3 per cent, highest renal blood flow is 868 ml. per minute. All cases are included in the means.

It will be remembered that glomerular filtration is a purely physical process dependent upon the intracapillary hydrostatic pressure and that, therefore, the proportion of plasma filtered (filtration fraction) will vary with the intracapillary pressure. The pressure within the glomerular capillaries can and does vary, depending upon the relative tonus of the afferent and efferent arterioles.

Let us assume that only one set of vessels change tonus at a time:

1. Constriction of the afferent arterioles (leading into the glomerulus) would: (a) diminish the renal plasma flow (diodrast clearance); (b) decrease the pressure distal to the constriction, in the glomerular capillaries, and the filtration would fall markedly; (c) decrease the filtration fraction because the filtration falls more, relatively, than does the plasma flow.

2. Constriction of the glomerular capillaries would: (a) diminish the renal plasma flow; (b) decrease the filtration; (c) not affect greatly the filtration fraction, because the intracapillary pressure is not much changed.

3. Constriction of the efferent arterioles would: (a) diminish the renal plasma flow; (b) increase the intravascular pressure proximal to the constriction, in the glomerular capillaries, and thus increase the filtration fraction; (c) maintain a normal filtration volume in the face of a deficit in plasma flow. (Smith and others<sup>20</sup> have demonstrated mathematically that filtration will remain constant when the volume of plasma flow is regulated by the tonus of the efferent arterioles, i.e., the filtration fraction will vary inversely as the plasma flow.)

Thus we see that the "male type" of essential hypertension is associated with constriction of the efferent arterioles. This explains why most clinical tests of renal function remain normal in uncomplicated essential hypertension, even though the renal plasma (and whole blood) flow may be reduced by as much as 50 per cent.

Having demonstrated that there is usually some reduction in the renal blood flow in posttoxemic hypertension, we were interested to know what might be found in posttoxemic women with normal blood pressures. In Table III are summarized the measurements made in 7 women, all of whom had had either eclampsia or severe preeclampsia within the past 1 to 4.2 years. In several of these cases the deficit in renal blood flow, as compared with average normal, is greater than that found in some of the hypertensives. In 2 cases, the filtration fractions are very low (possibly because of decreased glomerular permeability?). While none of these women is hypertensive, some degree of renal damage may be present in 5 of the 7. Perhaps hypertension itself prevents the appearance of more marked renal ischemia in the patients with high blood pressure; this has been more fully discussed elsewhere (Chesley and Chesley<sup>19</sup>).

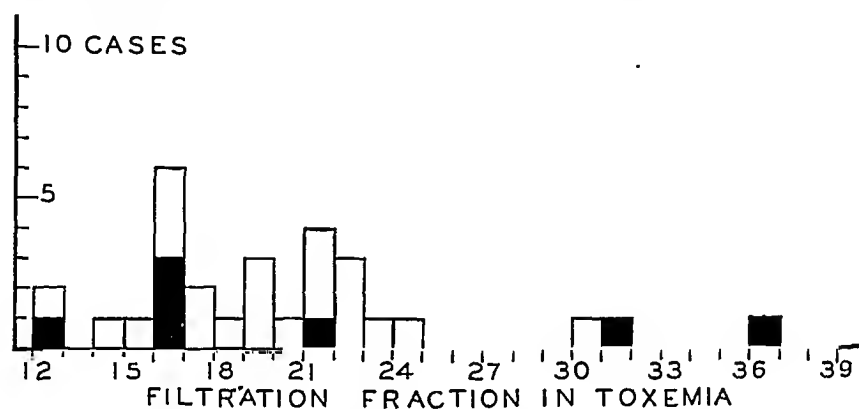


Chart 1.—The relation between the filtration fraction as measured at the height of toxemia and the presence or absence of hypertension (above 140/90) two years later. Black squares represent hypertensives; white squares represent patients with normal blood pressure.

#### RELATION OF THE FILTRATION FRACTION IN TOXEMIA TO SUBSEQUENT HYPERTENSION

We<sup>21</sup> have measured the renal blood flow during the acute phase of toxemia, and found that it is characteristically normal, although there is a wider range above and below average than we<sup>22</sup> found in normal women. In these toxemic women the filtration fractions vary widely, and many values are definitely abnormal. Fig. 1 shows the distribution of the filtration fractions as determined at the height of the acute toxemia. (Our findings as regards renal blood flow and filtration fractions in toxemia have recently been confirmed by Corcoran and Page,<sup>23</sup> and by Taylor<sup>24</sup>.)

We have re-examined all of our patients at twenty to twenty-four months after the measurement of renal function, and find a correlation between the filtration fraction as then determined and the blood pressure of today.

Following the argument outlined above, these patients may be divided into 3 groups on the basis of their filtration fractions during toxemia.

*Group A. Patients With High Filtration Fractions (Above 25 Per Cent).—*Women in this group exhibit the efferent arteriolar constriction characteristic of the "male type" of hypertension. Four such cases were observed (2 unpublished). Of these, 3 were known to have had hypertension antedating the first pregnancy, and now have elevated blood pressure at two years after delivery. In the fourth case, the pre-eclampsia was complicated by pyelitis which may have disturbed the renal hemodynamics; this patient is now normal.

*Group B. Patients With Low Filtration Fractions (Below 17 Per Cent).—*In the 10 patients showing lowered filtration fractions, it is presumed that glomerular

tain an *apparently* normal filtration fraction as estimated from the urea clearance, although the actual filtration fraction were elevated. Neither of these alternatives appeals to us so much as does the first explanation, which incriminates the capillaries.

Whether the posttoxemic hypertension is *caused* by the disturbance in renal hemodynamics cannot be finally decided at the present time. It seems logical to suppose that the narrowing of the capillary lumina might lead to hypertension. The probable mechanism of renal hypertension, as simplified from the publications of Page<sup>8</sup> might be summarized as follows:

1. Reduction in intrarenal pulse pressure (lessened difference between systolic and diastolic pressures *in the kidney*).
2. Release of renin from the kidney.
3. Activation of renin  $\rightarrow$  angiotonin (the pressor substance).
4. Generalized arteriolar constriction, *especially marked in efferent glomerular arterioles*.
5. Further reduction in the intrarenal pulse pressure (because of 4), thus establishing a vicious cycle which maintains hypertension.

Reduction in the lumina of the glomerular capillaries would, of course, offer an increased resistance to perfusion. This would result in an increased back-pressure, and thus the intrarenal diastolic pressure would be increased. The systolic pressure remaining constant, the intrarenal pulse pressure must be diminished. Such reduction in pulse pressure appears to be the stimulus for the release of renin from the kidney.

Posttoxemic hypertension seems not to fulfill one of the postulates (Number 4 in the above summary) in that the efferent arterioles do not *appear* to be constricted. If they really are not constricted, then this form of hypertension is not a typical renal hypertension. However, the efferent arterioles may be constricted, and the expected increase in filtration fraction not found because of diminished capillary permeability. We do not know whether the thickened basement membrane, if present, would be less permeable than normal. If its permeability were diminished, then the constriction of the efferent arterioles would be masked, since the increased intraglomerular pressure would be expended in maintaining a normal filtration fraction.

TABLE III. RENAL HEMODYNAMICS IN POSTTOXEMIC WOMEN WITH NORMAL BLOOD PRESSURES

AGE YEARS	POST PARTUM YEARS	BLOOD PRESSURE MM. HG	PLASMA CLEARANCE OF		CALCULATED GLOMERULAR FILTRATION ML./MIN.	FILTRA- TION FRACTION PER CENT	DEFICIT IN RENAL BLOOD FLOW PER CENT
			DIO- DRAST ML./MIN.	UREA ML./MIN.			
23	1.0	90/50	637	65.6	109	17.1	(-13)*
38	4.2	110/66	411	55.0	92	22.2	28
36	1.1	98/60	721	98.0	163	22.5	(-13)*
32	3.5	100/70	435	36.0	60	13.8	25
25	1.5	110/70	493	60.9	101	20.5	18
18	1.8	114/74	459	35.9	60	13.1	14
35	1.3	120/70	392	54.9	92	23.3	28

\*Renal blood flow 13 per cent above average normal of 850 ml. per minute.

# THE EFFECTS OF CERTAIN GONADOTROPIC EXTRACTS ON ANOVULATORY CYCLES AND AMENORRHEA

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**A**BNORMAL physiology of endocrine glands has become increasingly recognized in the past few years as an occasional cause of sterility in both the male and the female.

This abnormality may manifest itself in the female by anovulatory cycles which may not be recognizable by menstrual phenomena from normal ovulatory cycles.

The delicate interrelationship of the pituitary and ovary in producing endometrial changes and controlling menstruation and the apparent control of the pituitary over ovulation have led to the conclusion that the causative factor in at least certain cases of anovulation may be deficient pituitary activity. Therefore attempts are being made to stimulate ovulation in the anovulatory patient with various gonadotropic products.

Davis and Koff<sup>1</sup> first reported success in stimulating ovulation with the gonadotropic factor of pregnant mares serum in 1938 and later Siegler and Fein<sup>2</sup> duplicated their findings in a higher percentage of cases. None of the patients, however, were proved to be previously anovulatory. In other words, ovulation was observed in an ovary which might have been normally ovulating even without gonadotropic treatment.

On the other hand, Gray,<sup>3</sup> in a carefully controlled series of patients with abnormal menstruation and shown to be anovulatory, found some evidence of correction of irregularities, especially in amenorrhea, and occasional development of secretory endometrium following pregnant mares serum therapy.

Huber and Davis,<sup>4</sup> working with anovulatory patients, also produced secretory activity in some cases following pregnant mares serum administration and pregnancies occurred in a few instances.

Hartman,<sup>5</sup> using the *Macacus rhesus*, an animal which in captivity is physiologically anovulatory during certain months of the year and frequently anovulatory at other times, found that ovulation was *probably* induced in a small proportion (7 in 104) of animals injected with pregnant mares serum.

It is difficult to judge how frequently anovulatory menstruation occurs in the human being. This phenomenon was mentioned by Gardner<sup>6</sup> as early as 1856 as a possible cause for sterility in women. Rock, Bartlett and Matson<sup>7</sup> found 36 patients in a series of 392 who showed evidence of anovulation; Novak<sup>8</sup> found 39 in 142 cases, while Israel and Mazer<sup>9</sup> noticed 36 in 109.

Repeated biopsies and pregnanediol determinations on 83 sterility cases from a clinic in the Sloane Hospital for Women disclosed 7 patients who were consistently anovulatory and 2 others who had occasional anovulatory cycles. The menstrual cycles in some of these cases were irregular, but similar irregularity also occurred in patients who regularly developed secretory endometrium.

capillary damage is responsible for the disproportionate fall in glomerular filtration. Women showing such decreased filtration fractions in toxemia of pregnancy, therefore, have sustained more severe glomerular damage than have the patients having normal filtration fractions. *If toxemia of pregnancy causes subsequent hypertension, these women with low filtration fractions should show a high incidence of later hypertension.* As Fig. 1 indicates, 4 patients of 10 do have hypertension at follow-up. Whether the other 6 will eventually have hypertension, or be more susceptible to recurrence of toxemia we cannot yet say.

*Group C. Patients With Normal Filtration Fractions (17 to 25 Per Cent).*—In the 16 patients having normal filtration fractions during toxemia, glomerular damage might be considered as slight. At follow-up, only 1 of these patients was found to have hypertension, and she has had repeated toxemia.

In brief: of 16 patients having normal filtration fractions during toxemia of pregnancy, only 1, 6.3 per cent, is now hypertensive. Of 14 patients showing abnormal filtration fractions during toxemia, 7 or 50 per cent, are now hypertensive.

#### COMMENT

Regardless of the interpretations, admittedly speculative, the objective observation remains that laboratory methods will differentiate between posttoxemic and the "male type" of cardiovascular hypertension. While there are alternative possibilities, the findings are most plausibly explained on the basis of residual damage left by the toxemia, as described by Bell: "It may be said, therefore, that chronic renal disease may result from the acute lesion of eclampsia, but it is a special type differing from the known forms of chronic renal disease in its structure and pathogenesis. On the basis of the anatomical structure, one would expect to find hypertension and renal insufficiency clinically."

I desire to acknowledge my indebtedness to Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters who have read and criticized the typescript of this paper.

#### REFERENCES

- (1) Chesley, L. C., and Somers, W. H.: Surg., Gynec. & Obst. 72: 872, 1941. (2) Chesley, L. C., Somers, W. H., Gorenberg, H. R., and McGeary, J. A.: AM. J. OBST. & GYNEC. 41: 751, 1941. (3) Heynemann, T.: Zentralbl. f. Gynäk. 58: 3010, 1934. (4) Herrick, W. W., and Tillman, A. J. B.: Arch. Int. Med. 55: 643, 1935. (5) McKelvey, J. L., and MacMahon, H. E.: Surg., Gynec. & Obst. 60: 1, 1935. (6) Zimmerman, H. M., and Peters, J. P.: J. Clin. Investigation 16: 397, 1937. (7) Herrick, W. W., Tillman, A. J. B., and Grebenc, L.: AM. J. OBST. & GYNEC. 31: 832, 1936. (8) Corcoran, A. C., and Page, I. H.: J. A. M. A. 116: 690, 1941. (9) Löhlein, M.: Deutsche med. Wchnschr. 44: 1187, 1918. (10) Fahr, T.: Zentralbl. f. Gynäk. 44: 991, 1920. (11) Lubarsch, O.: In Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin, 6: 587, 1925. (12) Bell, E. T.: Am. J. Path. 8: 1, 1932. (13) Baird, D., and Dunn, J. S.: J. Path. & Bact. 37: 291, 1933. (14) Page, E. W., and Cox, A. J.: West. J. Surg., Obst. & Gynec. 46: 463, 1938. (15) Kellar, R. J., Arnott, W. M., and Matthew, G. D.: J. Obst. & Gynaec. Brit. Emp. 44: 320, 1937. (16) Kellar, R. J.: Ibid. 46: 462, 1939. (17) Smith, H. W., Goldring, W., and Chasis, H.: J. Clin. Investigation 17: 263, 1938. (18) Smith, H. W.: The Physiology of the Kidney, New York, 1937, Oxford University Press. (19) Chesley, L. C., and Chesley, E. R.: J. Clin. Investigation 19: 475, 1940. (20) Smith, H. W., Chasis, H., Goldring, W., and Ranges, H. A.: Ibid. 19: 751, 1940. (21) Chesley, L. C., Connell, E. J., Chesley, E. R., Katz, J. D., and Glisson, C. S.: Ibid. 19: 219, 1940. (22) Chesley, L. C., and Chesley, E. R.: Am. J. Physiol. 127: 731, 1939. (23) Corcoran, A. C., and Page, I. H.: Am. J. M. Sc. 201: 385, 1941. (24) Taylor, H. C.: J. Clin. Investigation. In Press.



usually absent, and in Case 7 it may possibly be due to the fact that there are occasional twenty-four-hour lapses even in normal excretion.<sup>11</sup>

In the above cases, evidence of ovulation occurred occasionally following gonadotropic therapy. It is a question whether or not this therapy has actually caused the subsequent ovulation either in these

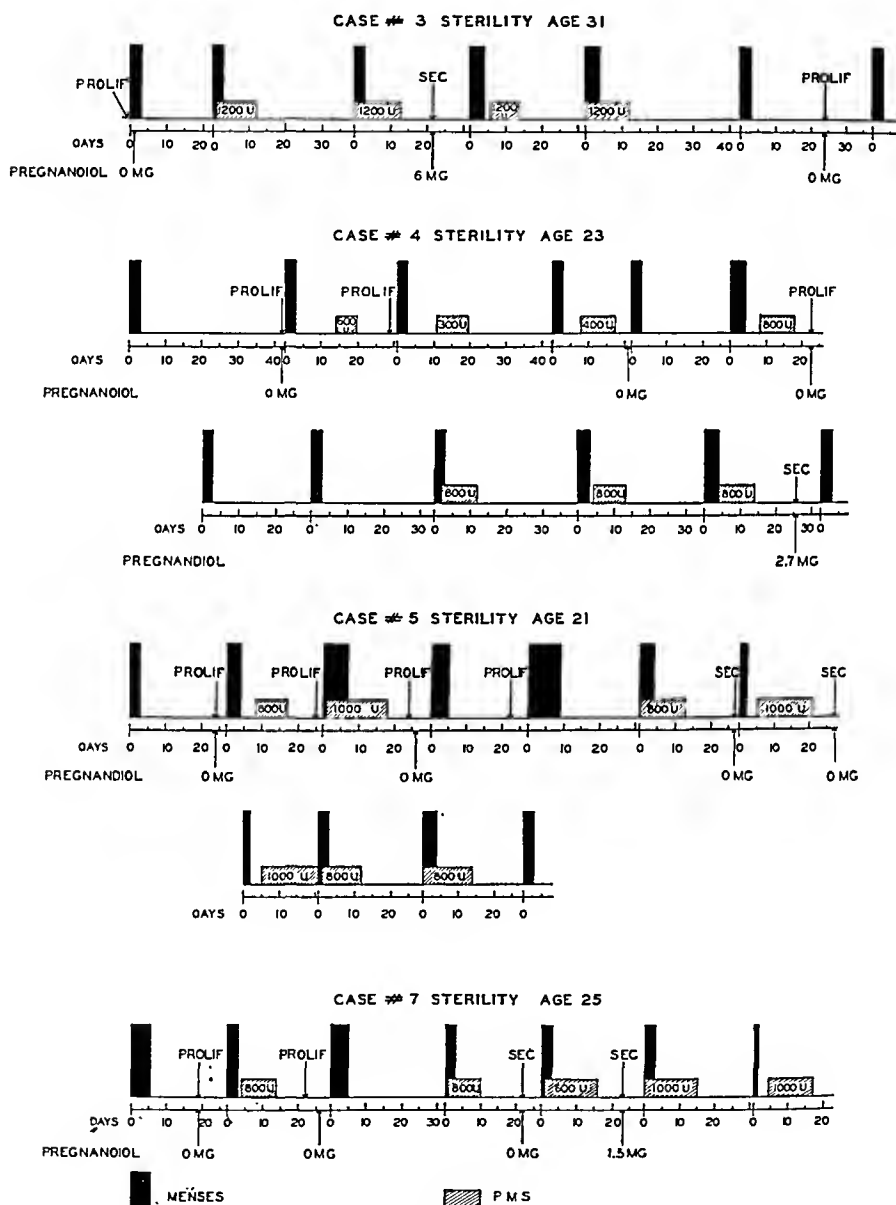


Fig. 1.—Four cases showing evidence of ovulation during courses of pregnant mares serum administration. Arrows pointing downward represent endometrial biopsy with diagnosis of proliferative or secretory endometrium as indicated.

cases or similar ones reported elsewhere in the literature. It is a well-known fact that many untreated women ovulate sporadically even though menstruating regularly,<sup>7, 8, 12</sup> just as the above treated patients

If the above figures are taken as a group, the percentage of anovulation in women complaining of sterility is about 16. It would be incorrect to conclude, however, that 16 per cent of sterility is caused by anovulation, as many of the above cases doubtless have other sterility stigmas, but at the same time the percentage is high enough to demand consideration of anovulation as a significant sterility factor.

Any investigation concerning the problem of ovulation obviously requires accurate methods for the diagnosis of this phenomenon. Since it is generally supposed that the formation of a corpus luteum occurs only after ovulation, and since it is possible to obtain evidence of luteal secretion, the most accurate diagnosis of ovulation at the present time rests largely on the evidence of activity of the corpus luteum. This evidence is obtainable not only from the endometrium by biopsy, but also from the urinary excretion of pregnanediol. This substance, shown by Venning<sup>10</sup> to be an excretion product of the corpus luteum hormone, progesterone, is susceptible to quantitative chemical identification. Therefore, it seems justifiable to assume that ovulation has occurred if either one, or better both, of these tests are positive, although there could be a rare exception due to imprisonment of the ovum in the ruptured follicle.

#### MATERIAL

Ten patients (7 from the clinic of the Sloane Hospital for Women, 3 from private practice), who were judged to be anovulatory by the above methods of diagnosis, were treated with various quantities and types of gonadotropic extracts. In most cases pregnant mares serum extract (Gonadin, Cutter) and in a few cases pregnancy urine extract plus whole pituitary synergist (Synapoidin, Parke Davis & Co.) were used. In all cases these patients had the conventional sterility investigation, consisting of history, physical examination, urinalysis, blood count. Wassermann, basal metabolic rate, blood cholesterol, Rubin test, examination of husband, etc. Abnormalities other than anovulation are noted if present.

Pregnant mares serum or the synergist product was administered for the most part during the first two weeks of the menstrual cycle, usually in four dosages of 1 c.c. each (200 Cole-Saunders units of pregnant mares serum per c.c.), although there were occasional variations which will be mentioned in specific instances. Huber and Davis<sup>4</sup> injected intramuscularly 20 Cortland-Nelson units (equal to 200 Cole-Saunders units) of pregnant mares serum on each day from the seventh to tenth days and 60 units intravenously on the eleventh day. Gray<sup>3</sup> favored a similar technique using somewhat smaller dosages.

#### RESULTS

Four cases showed evidence of ovulation following prolonged administration of gonadin (Fig. 1). It will be observed that the gonadin dosage varied somewhat in the different menstrual cycles and that the cycles themselves were quite irregular. When evidence of ovulation was observed following therapy, it was noted that, in every case but one (Case 5), treatment had been started during menstruation and stopped at about the theoretical time of ovulation. Although this may be of no significance, it is remarked upon because the time relationship between the menstrual cycle and the date of administration has been considered extremely important.

The patients in Cases 5 and 7 in our series (Fig. 1) had been subjected to previous gynecologic operations elsewhere, involving, in the first case, unilateral oophorectomy, and in the second unilateral oophorectomy and partial resection of the other ovary. In these latter two cases no, or practically no, pregnanediol was present, even though secretory endometrium was found. In Case 5 this was because the specimens were collected the day before the onset of menstruation, when pregnanediol is

One of these (Case 16, Fig. 3) menstruated irregularly for a year (and possibly longer) following treatment, whereas previously she had suffered from amenorrhea for eight months. She did not conceive, however, and her periods of bleeding were totally irregular.

The other patients thought to have reacted to gonadotropic stimulation presented an interesting phenomenon diagnosed as primary pituitary failure due to an unknown cause at the age of 31 years. She complained of oligomenorrhea, menstruating about three times a year, headaches, severe hot flushes, 36 pounds' gain in weight in one year, polydipsia and polyuria and a four-year history of sterility. Treatment and complete laboratory workup were negative. Urine extraction for follicle-stimulating hormone showed none to be present (contrary to the picture seen in menopausal urine); x-ray of the sella turcica showed no abnormalities and repeated basal metabolism rate determinations were normal.

She received 7 c.c. of pregnancy urine plus pituitary synergist over a period of twenty-six days, and pregnancy was evident about six weeks following the first injection. She later delivered uniovular twins.

#### CASE #20 STERILITY AGE 21

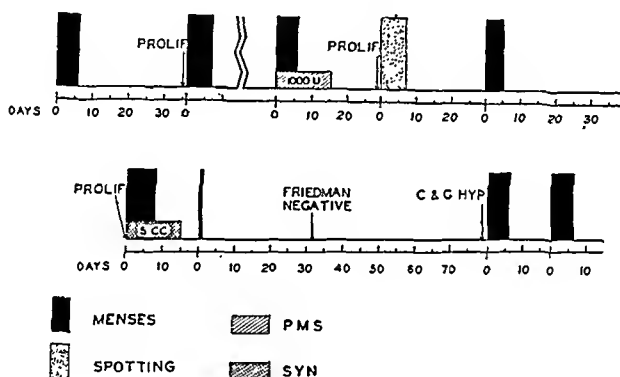


Fig. 4.—One patient who developed amenorrhea and ovarian cyst formation following gonadotropic therapy. Proliferative and cystic-glandular hyperplastic endometriums are diagnoses of tissue obtained by biopsy.

None of the other amenorrheic cases was benefited in the slightest by the treatment even after bleeding had been stimulated by estrogens.

Possible harmful effects of gonadotropic stimulation of the ovary may occur. Smith, Kurzrok and Watson<sup>13</sup> demonstrated ovarian cyst formation following large dosage of pregnant mares serum, and Hartman<sup>5</sup> has observed this phenomenon in the monkey. Case 20 (Fig. 4) developed amenorrhea following pregnancy urine-synergist treatment in conjunction with a gradually enlarging adnexal mass thought to be an ovarian cyst. Subsequent biopsy disclosed cystic glandular hyperplasia of the endometrium and following a period of bleeding the adnexal mass disappeared. It was thought that in this case stimulation of estrogen production was so great that bleeding was prevented by excessive estrogen secretion and that ultimately bleeding resulted as an estrogen withdrawal phenomenon.

The significance of antihormone development following pregnant mares serum administration is as yet unknown. Meyer and Wolfe<sup>14</sup> observed antigonadotropic activity following injection of even small amounts of pregnant mares serum in the monkey, and this phenomenon was found by Jailer and Leathem<sup>15</sup> to occur also in the human being. There is as yet no evidence to show that this antihormone production is inhibitory to the patient's own gonadotropins.

#### SUMMARY

Sterile patients with either anovulatory menstruation or amenorrhea were treated with the gonadotropic extracts from pregnant mares serum

have done. Fig. 2 describes two patients of this type. The patient in Case 8 received thyroid therapy throughout the period of investigation, a fact which might conceivably explain the second ovulatory period but not the first.

Therefore, in patients previously treated with pregnant mares serum, we can by no means be certain that ovulation was a result of this treatment, for it might have occurred without treatment.

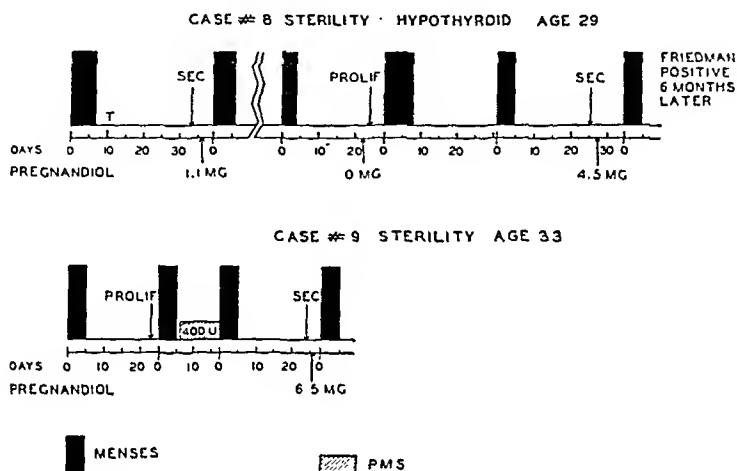


Fig. 2.—Two cases showing evidence of occasional ovulation without treatment. Arrows pointing downward represent endometrial biopsy with diagnosis of proliferative or secretory endometrium as indicated. "T" in Case 8 represents the beginning of thyroid therapy.

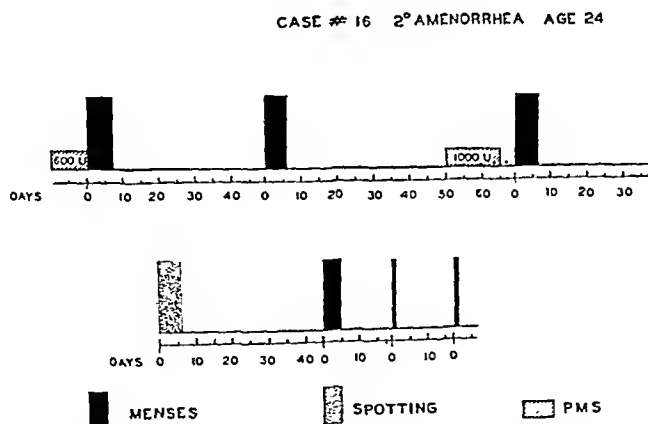


Fig. 3.—One patient with amenorrhea of eight months who had irregular periods of bleeding following pregnant mares serum therapy.

In addition to the use of the gonadotropic factor on the anovulatory patient, this substance was administered to patients complaining of secondary amenorrhea. These patients were also sterile but without other demonstrable abnormalities. Cases of amenorrhea in the absence of other symptoms have not been treated unless pregnancy is desired. Two patients of 10 treated are thought to have shown a possible reaction to therapy.

# ARE ESTROGENS CARCINOGENIC IN THE HUMAN FEMALE?

## II. ATYPICAL ENDOMETRIAL PROLIFERATION IN A PATIENT TREATED WITH ESTROGENS

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SINCE the widespread use of estrogens in recent years, the relationship of estrogens to carcinogenesis, has become a problem of great importance to the clinician. The original report of Lacassagne,<sup>1</sup> of the production of mammary carcinoma in male mice bred from female mice with a high incidence of spontaneous mammary carcinoma, has been amply confirmed.<sup>2</sup> Loeb<sup>3</sup> concluded that both genetic and hormonal factors have important roles in the production of mammary carcinoma. This conclusion is supported by the fact that mammary carcinoma has thus far been produced by estrogens only in inbred male mice from "high tumor" strains. Metaplasia of the epithelium of the cervix has been produced following the administration of estrogens plus trauma in monkeys<sup>4</sup> and guinea pigs.<sup>5</sup> In mice, Gardner, Allen, and Smith<sup>6</sup> have reported carcinomatous lesions of the cervix following estrogen injections. In the human being, Allasen and Owen,<sup>7</sup> and Auchincloss and Haagensen<sup>8</sup> have reported the occurrence of adenocarcinoma of the breast in patients treated with estrogens. On the other hand, we could find no evidence of abnormal proliferation in the endometrial or vaginal mucosa<sup>9</sup> in a series of 206 patients who had been treated with huge doses of estrogens over periods of time extending to five and one-half years.

The possibility of estrogens having carcinogenic potency in human beings is fraught with such serious implications that all cases, in which there appears to be some such relationship, should be investigated very thoroughly. Here we wish to report a case which illustrates this problem.

### CASE REPORT

The patient was a 52-year-old, gravida iii, para ii, who was admitted to the Gynecological Clinic of the Mount Sinai Hospital, in June, 1938, complaining of menopausal symptoms of two years' duration. Her last menses had occurred two years prior to admission. The past history was irrelevant. The available family history revealed no predisposition or tendency to carcinoma. The father had died of a strangulated hernia at the age of 53. The mother had died at the age of 70. The cause of death was unknown. One brother and sister are alive and well. The patient's husband had died of cancer of the stomach. Pelvic examination revealed a parous introitus; the vagina was uninflamed. The cervix was lacerated and the uterus was slightly enlarged by the presence of small fibroids. The adnexa were not palpable. From June 20, 1938, to Aug. 5, 1938, the patient received 40,000 R.U. of  $\alpha$ -estradiol benzoate. There was no immediate withdrawal bleeding. Several months later, on Dec. 21, 1938, spontaneous uterine bleeding occurred. Examination revealed a small cervical polyp which was removed. The endometrium, obtained at

(gonadin, Cutter) or pregnancy urine plus pituitary synergist (synapoidin, Parke Davis & Co.).

# CONCLUSIONS

1. Ovulation may have been caused in 4 previously anovulatory cases by pregnant mares serum, although this is not conclusive because other previously anovulatory cases were observed who ovulated without treatment. There were no pregnancies following the use of pregnant mares serum.

2. One patient complaining of amenorrhea for eight months menstruated irregularly for at least one year following pregnant mares serum treatment.

3. One patient diagnosed as having primary pituitary insufficiency became pregnant following pregnancy urine-pituitary synergist treatment. This is the only pregnancy in this series.

4. Possible harmful effects of gonadotropic stimulation, such as ovarian cyst formation and antihormone production, may occur. One patient treated with pregnancy urine-pituitary synergist developed amenorrhea and an ovarian cyst. Menstruation occurred and the cyst regressed following cessation of treatment.

It is impossible at this time to say whether or not the above evidences of ovulation are due to coincidence or to the results of treatment. Certainly the time sequence in the "successful" cases indicates a cause and effect relationship. It must be remembered that these cases were "successful" only so far as evidence of corpus luteum activity occurred. No pregnancies resulted in the patients receiving pregnant mares serum treatment.

The evidence for the induction of ovulation by pregnant mares serum or pregnancy urine-pituitary synergist is therefore suggestive but by no means conclusive.

The gonadotropic substances used were pregnant mares serum extract (Gonadin, Cutter) and pregnancy urine extract plus whole pituitary synergist (Synapoidin, Parke, Davis & Co.). These substances were supplied through the courtesy of Dr. Donald H. Wonder of Cutter Laboratories and of Dr. E. A. Sharp of Parke, Davis & Company.

I wish to express my gratitude to Dr. B. P. Watson, Director of the Sloane Hospital for Women, and to Dr. Earl T. Engle, Professor of Anatomy, Columbia University, College of Physicians and Surgeons, for their helpful advice and suggestions during the course of this study.

# REFERENCES

- (1) Davis, M. E., and Koff, A. K.: AM. J. OBST. & GYNEC. 36: 183, 1938. (2) Siegler, S. L., and Fein, M. J.: Ibid. 38: 1021, 1939. (3) Gray, L. A.: South. M. J. 33: 160, 1940. (4) Huber, C. P., and Davis, M. E.: Surg., Gynec. & Obst. 70: 996, 1940. (5) Hartman, C. G.: Bull. Johns Hopkins Hosp. 63: 351, 1938. (6) Gardner, A. K.: Sterility; Causes and Curative Treatment, New York, DeWitt and Davenport, p. 28. (7) Rock, J., Bartlett, M. K., and Matson, D. D.: AM. J. OBST. & GYNEC. 37: 3, 1939. (8) Novak, E.: Ibid. 35: 605, 1939. (9) Israel, S. L., and Mazer, C.: Ibid. 36: 445, 1938. (10) Fenning, E. H.: J. Biol. Chem. 119: 473, 1937. (11) Burton, C. L.: AM. J. OBST. & GYNEC. 40: 202, 1940. (12) Westman, A.: Geburtsh. u. Frauenh. 1: 321, 1939. (13) Watson, B. P., Smith, P. E., and Kurzrok, R.: AM. J. OBST. & GYNEC. 36: 562, 1938. (14) Meyer, R. K., and Wolfe, H. R.: J. Immunol. 37: 91, 1939. (15) Jailer, J. W., and Leatham, J. H.: Proc. Soc. Exper. Biol. & Med. 45: 506, 1940.

65 mg. of progesterone. The latter hormone was given in divided doses during the last ten days of this course of injections. Prior to the administration of the progesterone, an endometrial biopsy revealed an advanced proliferative endometrium with areas of cystic hyperplasia. Following the administration of the progesterone, the endometrium revealed a mixed picture of proliferative and advanced secretory

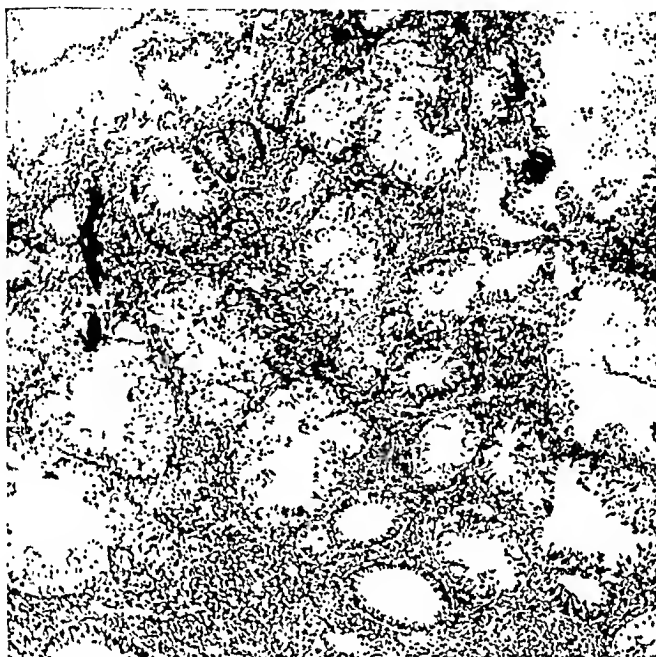


Fig. 3, A.—Endometrial biopsy (No. 72063—Sept. 9, 1940), approximately five and one-half months postimplantation. Note numerous glands with stratification and budding. Some glands contain leucocytes and desquamated epithelial cells. ( $\times 105$ .)

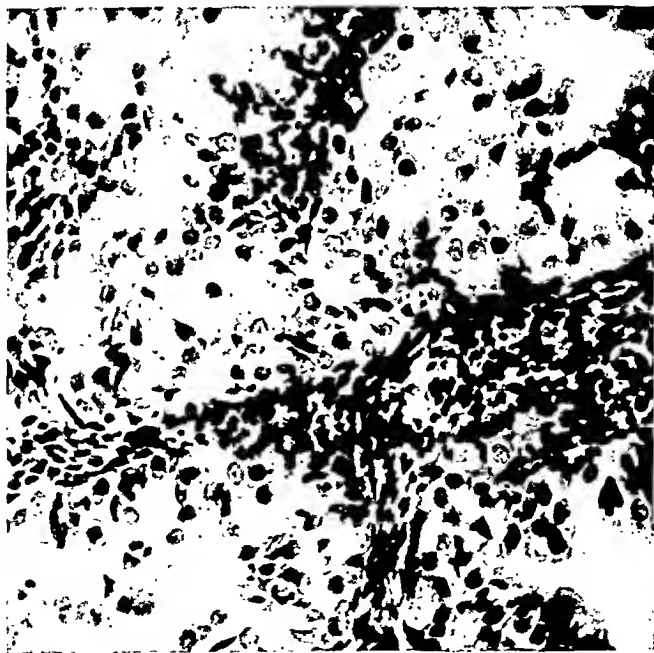


Fig. 3, B.—Higher power magnification of Fig. 3, A. ( $\times 425$ .)

the same time by suction curettage, showed a variable picture with areas of moderate proliferation interspersed with areas of hypoplasia.

Because of a recurrence of the menopausal symptoms, estrogen therapy was resumed in January, 1939. From Jan. 4 to Feb. 7, 1939, this patient received 234,000 R.U. of  $\alpha$ -estradiol benzoate, administered intramuscularly, in addition to

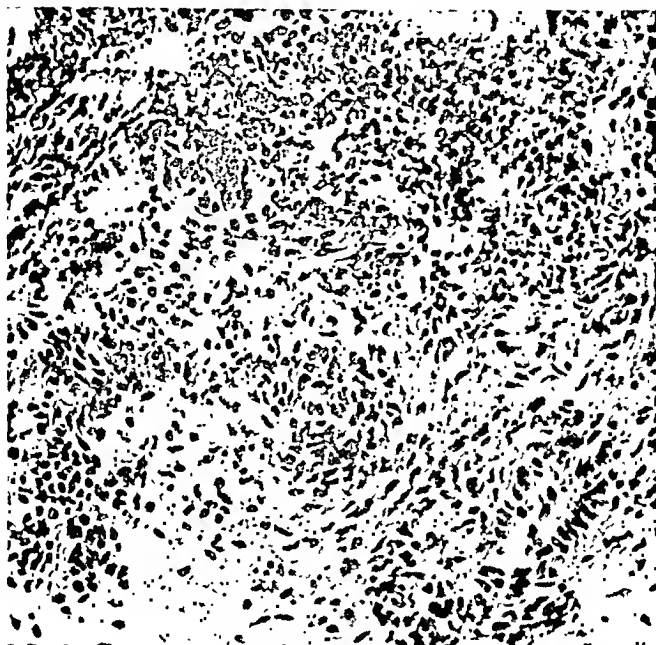


Fig. 1.—Endometrial biopsy (No. 69072—March 20, 1939). Note advanced atrophy; only 3 small shrunken glands surrounded by an inactive stroma. ( $\times 285$ .)

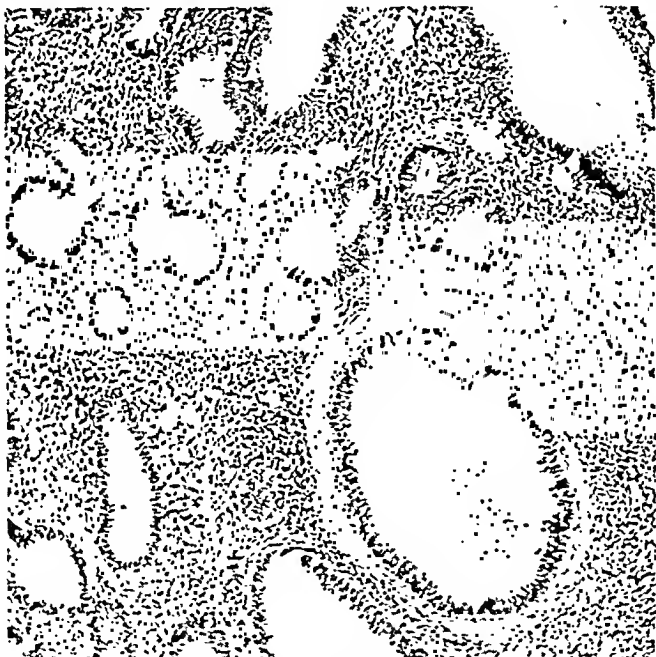


Fig. 2.—Endometrial biopsy (No. 71098—June 17, 1940), approximately three months after implantation. Note persistent estrogenic effect; numerous proliferating glands with several large, dilated glands, consistent with diagnosis of slight hyperplasia. ( $\times 103$ .)



months after the implantation of the  $\alpha$ -estradiol pellet, the implantation site was excised.<sup>10</sup> Endometrial and vaginal biopsies were taken at the time of excision and revealed morphologic regression to the pre-implant status, viz., atrophy of the endometrium (Fig. 1) and evidence of estrogen deficiency in the vaginal biopsy. At this time, the patient was re-implanted with 29 mg. of loose crystals of  $\alpha$ -estradiol benzoate. Six weeks after this implantation, moderate uterine bleeding occurred and intermittent spotting persisted for approximately six weeks. At the end of this time (June 17, 1940), an endometrial biopsy showed advanced proliferation with numerous dilated glands (Fig. 2). Five days after the suction curettage, the bleeding stopped, only to recur on Sept. 9, 1940. At this time, another endometrial biopsy was obtained by suction curettage and revealed a variable endometrial pattern. In some areas, the endometrial glands and stroma were atrophic, whereas, in other areas, there was evidence of moderate proliferative activity with several dilated, cystic glands. In addition, one small fragment of endometrium revealed several closely packed glands which were lined by large, pale, epithelial

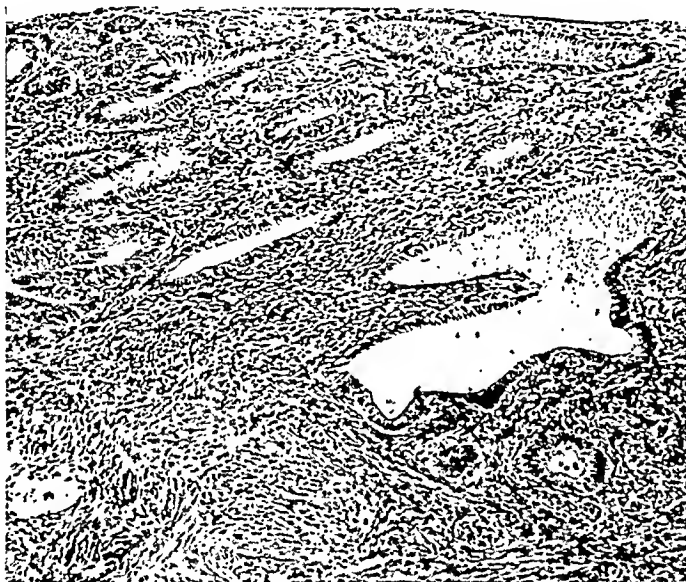


Fig. 5.—Endometrium of extirpated uterus (No. 72509—Oct. 17, 1940) showing moderate proliferation and a few dilated cystic glands. Note no evidence of neoplastic change. ( $\times 103$ .)

cells with ovoid nuclei and increased amounts of cytoplasm containing large vacuoles. These cells showed marked pseudostratification and in some glands the entire lumen was obliterated by sheets of cells (Figs. 3, *A* and *B*).

Up to this time, the patient had had 7 endometrial and vaginal biopsies and in no instance had there been any evidence of abnormal cellular proliferation or atypism. Following the last suction curettage, slight uterine bleeding continued. It is pertinent to note here that, although we have often noted uterine bleeding following implantation of estrogens, the bleeding is usually of short duration and frequently stops immediately after a suction curettage. In view of the abnormal type of bleeding and the atypical glandular changes noted in the endometrium, a diagnostic curettage, under anesthesia, was performed on Oct. 8, 1940, approximately one month after the last suction curettage.

Following microscopic examination of the curettings, a diagnosis of adenocarcinoma of the uterus was made by Dr. Paul Klemperer, pathologist at the Mount Sinai Hospital. This opinion was based on "the fact that the glands are very closely approximated with very little intervening stroma; that the epithelial cells show stratification and many mitotic figures" (Figs. 4, *A* and *B*).

phenomena. The patient received no treatment for approximately six months and, on June 20, 1939, a single pellet of crystalline  $\alpha$ -estradiol (25 mg.) was implanted subcutaneously in the right thigh because of the return of severe evidence of estrogen deficiency. The patient was apparently relieved of her symptoms and did not return to the follow-up clinic until seven months later. At this time, she complained of a recurrence of menopausal symptoms. On March 20, 1940, approximately nine

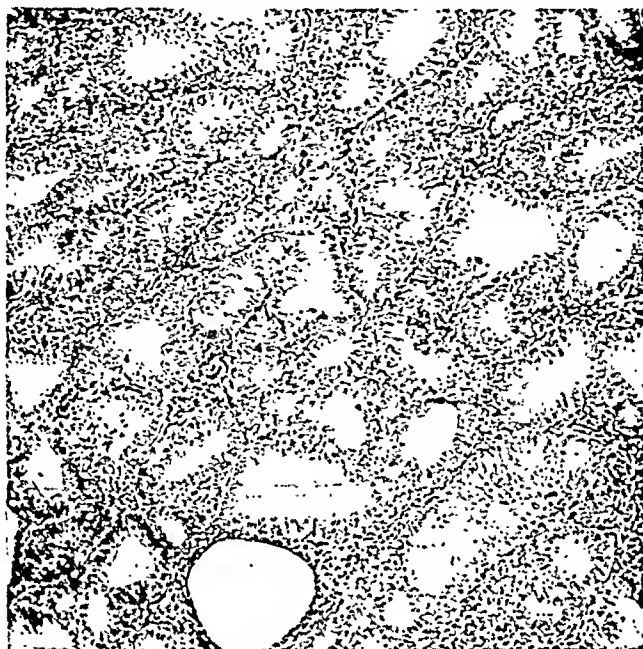


Fig. 4, A.—Endometrial biopsy (No. 72426—Oct. 8, 1940), approximately six and one-half months postimplantation. ( $\times 110$ .)

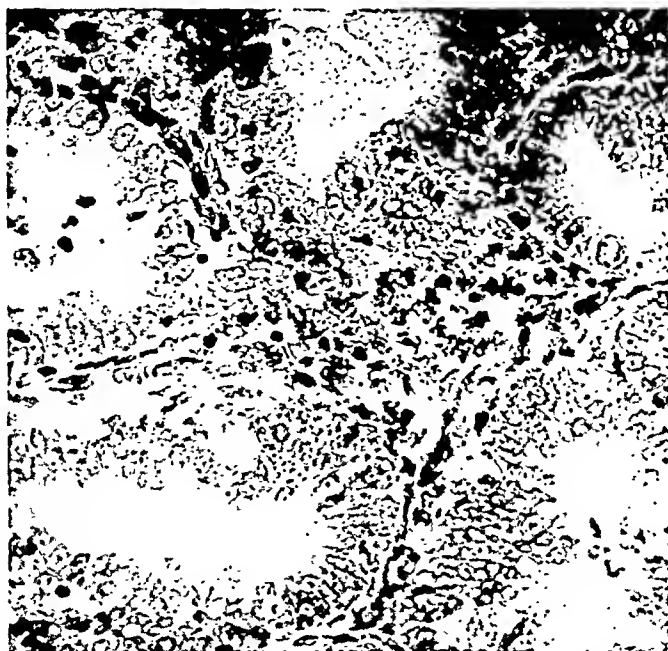


Fig. 4, B.—Higher power magnification of Fig. 4, A. Note increased number of mitotic figures; close approximation of glands with diminished intervening stroma; epithelial stratification. ( $\times 425$ .)

## REFERENCES

- (1) *Lacassagne, A.*: Compt. rend. acad. de Sc. 195: 630, 1932. (2) *Gardner, W. U., Smith, G. M., Allen, E., and Stray, L. C.*: Arch. Path. 21: 265, 1936. (3) *Loeb, C.*: Surg., Gynec. & Obst. 25: 300, 1917. (4) *Overholser, M. D., and Allen, E.*: Proc. Soc. Exper. Biol. & Med. 30: 1322, 1935. (5) *Nelson, W. O.*: Anat. Rec. 688: 99, 1937. (6) *Gardner, W. U., Allen, E., Smith, G. M., and Stray, L. C.*: J. A. M. A. 110: 1182, 1938. (7) *Allasen, G. E., and Owen, S. E.*: J. A. M. A. 112: 1933, 1939. (8) *Auchincloss, H., and Haagenzen, C. D.*: J. A. M. A. 114: 1517, 1940. (9) *Geist, S. H., and Salmon, U. J.*: AM. J. OBST. & GYNEC. 41: 29, 1941. (10) *Geist, S. H., Walter, R. I., and Salmon, U. J.*: Proc. Soc. Exper. Biol. & Med. 43: 712, 1940. (11) *Novak, E.*: Gynecological and Obstetrical Pathology, Philadelphia, 1940, W. B. Saunders Co. (12) Personal communication.

## CERVICAL DYSTOCIA\*

## A STUDY OF EIGHTY-SIX CASES

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IN CONSIDERING abnormal labor most textbooks devote little space to cervical dystocia and many authorities question its existence. The failure of prompt cervical dilatation is attributed either to cephalopelvic disproportion, to abnormal presentation, position, or attitude of the fetus, or to uterine inertia as a consequence of prematurity, toxemia, endocrine or medical infirmities. Yet a subsequent labor may be rapid and easy despite repetition of the same circumstances.

The following report is an attempt to determine the true frequency of cervical dystocia together with an analysis of the possible causative factors, clinical course, treatment, and end-results. For this study cervical dystocia is defined as difficult labor due principally to failure of the cervix to dilate and to be effaced within reasonable time despite frequent and forceful uterine contractions. Implied in this definition is the absence of those common causes of dystocia noted in the preceding paragraph.

## MATERIAL

Among 8,213 confinements at the Woman's Hospital during the six years 1930 to 1935 inclusive, only 86 cases satisfied the above criteria, an incidence of 1.05 per cent (Table I). Of 382 prolonged labors, thirty-six hours or more, cervical dystocia was the major cause in 51 cases, or 13.4 per cent. On critical re-study it was accepted as the major indication for 45 out of 474 cesarean sections (9.5 per cent), 2 out of 34 high forceps (5.9 per cent), 28 out of 778 medium forceps (3.6 per cent), and 9 out of 591 low forceps operations (1.7 per cent).

Many other "cervical dystocia" histories were excluded because the evidence was insufficient to rule out disproportion, malposition, or inertia. On the other hand some cases of transverse and posterior oc-

\*Read, by invitation, at a meeting of the Richmond Academy of Medicine, Richmond, Virginia, November 12, 1940.

On Oct. 16, 1940, a hysterectomy was performed. The uterus was normal in size and contained 2 small myomas and a small endometrial polyp. Several strips of endometrium were examined histologically and showed no evidence of carcinoma, metaplasia, or cellular atypism (Fig. 5).

#### DISCUSSION

As noted above, the extirpated uterus did not reveal any evidence of adenocarcinoma. The question arises as to the validity of the diagnosis of adenocarcinoma in the endometrial biopsies obtained prior to hysterectomy. After careful histologic study and re-evaluation of the clinical course, we believe that we were dealing with an atypical, but benign, endometrial lesion. This opinion is based upon the following: (a) The gland patterns showed only slight variation from normal. (b) There was no evidence of invasion of the stroma. (c) Pseudostratification and an increased number of mitotic figures occur normally in the proliferative phase of the menstrual cycle, as well as in endometriums stimulated by exogenous estrogens. (d) The gland pattern showed a relatively uniform regular appearance with an absence of "lawlessness" of tissue growth, which is associated with carcinoma.

However, it cannot be denied that the pathologic picture encountered is one which would immediately make the pathologist suspect carcinoma. It is apparent that the borderline histologic characteristics of the lesion permits of dual interpretation and, therefore, it was felt advisable to have some other opinions. Accordingly, the microscopie sections were sent to Dr. Robert Meyer, of the University of Wisconsin, Dr. Emil Novak, of Johns Hopkins University, and Dr. Herbert Traut, of Cornell University. Drs. Meyer and Novak were of the opinion that the lesion was benign. Dr. Traut was in agreement with Drs. Paul Klemperer and Sadao Otani, of the Mount Sinai Hospital, and considered the lesion to represent an early adenocarcinoma of the endometrium. Evidently, judged by histologic criteria alone, the question of the neoplastic character of the lesion cannot be categorically answered.

Another question which remains to be answered is the relationship of the administered estrogens to the endometrial lesion. Can we assign to estrogens an etiologic role in this case? We believe that the question should be answered in the negative for the following reasons: First, the localization of the atypical endometrial pattern to such a small area of endometrium makes it unlikely that the atypism was due to so general a stimulating agent as estrogens. If the opposite were true, we might expect multiple foci of abnormal change. Second, endometrial patterns, as described in this case, have been reported by Novak<sup>11</sup> as occurring spontaneously in postmenopausal women. These patients have been observed for several years and have not developed carcinoma of the uterus.<sup>12</sup>

In conclusion, it is suggested that extreme caution be used before attributing carcinogenic properties to estrogens in human beings, lest an extremely valuable therapeutic agent be condemned unjustly.

For the estrogens used in this investigation, we are indebted to Dr. Erwin Schwenk, of the Schering Corporation, Bloomfield, N. J.

parenchyma following trauma or disease. This fibrosis also obviously hinders *passive* dilatation by the bag of waters and presenting part.

Evidence supporting both concepts of pathogenesis is found in Table II.

The average age was 28.3 years, 13 patients being over 35 years of age. There was no familial or racial preponderance. In 78 out of 86 cases, this was the first full-term pregnancy. Late onset, irregularity or pain with the menses occurred in about one-fifth of the series. Eight patients had sought advice or been operated upon for sterility; and the interval between marriage and the present pregnancy was prolonged in nearly one-half of the cases. Various operations on the cervix had been done in 15 instances; abortion had been induced in 7 women while 5 others had had spontaneous abortions.

Of the 8 multiparas 4 gave a history of previous cervical dystocia; and cervical lacerations or tough scars were observed ante partum in 7 cases, chronic cervicitis in eight others. Fibrosis following fourteen x-ray treatments for menorrhagia in one case, and a cervical fibromyoma in another were thought to hinder dilatation. Thirteen patients had an underdevelopment of the cervix, five being associated with constricted vagina.

Gonorrheal cervicitis does not necessarily lead to cervical dystocia. A patient of the writer, contracting acute infection in the sixth month of her first pregnancy, went into labor at thirty-nine weeks, was fully dilated within eleven hours and was soon delivered of a 7 pound 12 ounce child. Three years later a second labor was completed in five hours.

The foregoing ante-partum data are derived from 49 of the 86 case charts, some of the remainder being doubtless incomplete. The frequency of the various causative factors may therefore be greater than that suggested by Table II. Certainly the descriptions of the cervix during labor, as summarized in Table III, indicate local pathology in a much larger proportion of the cases. Also as shown in Table VI, cervical dystocia was repeated in subsequent confinements of 3 out of 20 patients, an incidence of 15 per cent compared to the incidence of 1.05 per cent for all confinements.

#### CHARACTER OF LABOR AND DESCRIPTION OF CERVIX

In Table III an attempt is made to group the data from 86 labor records.

The first stage of labor averaged 38 hours 57 minutes and lasted over thirty hours in 61 cases. The entire labor exceeded 36 hours in 51 cases. Contractions were very strong in 71 patients, moderately strong in 8 others. In only 3 of the 82 reported were they called weak; and in 59 out of 82 they occurred at regular intervals. Their duration was more than 30 seconds in 55, over 50 seconds in 45 cases out of 56 reported.

Various adjectives were used to describe the cervix which was pathologic in type, or abnormal in behavior in every one of the 86 cases. Full dilatation was finally achieved in only 19 patients, and 10 cm. in an additional 7. In the remaining 60 women, intervention was necessary with the cervix dilated from nothing to 9 cm.

#### DIAGNOSIS

Cervical dystocia was suspected if, notwithstanding frequent contractions, definite progress had not occurred in a reasonable time. This presumption was strengthened by a history or clinical findings of disease, injury or underdevelopment of the cervix; and confirmed when examination excluded primary uterine inertia, cephalopelvic disproportion and unalterable abnormal presentation, position and attitude of the fetus. Abdominal and rectal examinations often gave misleading impressions.

TABLE I. INCIDENCE OF CERVICAL DYSTOCIA DURING SIX YEARS 1930-1935 INCLUSIVE

	TOTAL CASES	CERVICAL DYSTOCIA	
		CASES	PERCENTAGE
Viable confinements	8,213	86	1.05
Prolonged labors	382	51	13.4
Cesarean sections	474	45	9.5
High forceps	34	2	5.9
Medium forceps	778	28	3.6
Low forceps excluding prophylactic	591	9	1.7

eiput were included, for instance when subsequent delivery of an equally large baby was rapid and easy despite repetition of the malposition. Certain history charts were accepted only after discussion with the responsible surgeon. But with due allowance for a large personal element in judging each case, the above figures indicate trouble with the cervix as the major factor in a small but definite proportion of abnormal labors.

#### ETIOLOGY

Those who admit the existence of cervical dystocia offer two general explanations of its origin. The first points to constitutional deficiency manifested by obesity, lack of normal feminine habitus, endocrine dyscrasias, disturbances of menstruation and fertility, and maldevelopment of the vagina, cervix, and corpus uteri. The second theory stresses rigidity and stenosis of the cervix as a result of fibrosis following operative or obstetric trauma, abortions and infections. Since *active* dilatation, retraction, and effacement of the cervix depend upon its intrinsic smooth muscle and autonomie nerves, this function may be weakened by underdevelopment, constitutional and endocrine deficiency. It is further compromised and resisted by scar tissue replacement of the

TABLE II. ETIOLOGIC FACTORS IN CERVICAL DYSTOCIA, 86 CASES

Parity: First full-term pregnancy in 78 cases
Age: 35 years or more in 13 cases. Average 28.3 yr.
Late menarche:
At or after 15 years: 20
At or after 16 years: 11
Irregular menses: 5. Severe dysmenorrhea: 7
Sterility (complaint or operation): 8
Interval between marriage and present pregnancy
Over 2 years: 42      Over 3 years: 27
Over 4 years: 17      Over 5 years: 11
Abortions: 12 patients. Induced in 7, spontaneous in 5
Previous operations on cervix: 15
Previous cervical dystocia: 4 (out of 8 multiparas)
Previous radiation: 1 (14 x-ray treatments for menorrhagia)
Maldevelopment and disease noted antepartum
Marked obesity: 3      Hypopituitary type: 2
Masculine pelvis (but no disproportion): 4
Vagina constricted, underdeveloped: 5
Infantile cervix: 13, with pinhole os in 3 cases
Chronic cervicitis and/or erosion: 8
Laceration and scarring: 7, with cervicovaginal band in 2 cases
Cervical fibromyoma: 1

TABLE IV. AIDS TO CERVICAL DILATATION

<i>Stimulation:</i>		<i>Sedation and analgesia:</i>	
Enemas, 81		Morphine and scopolamine, 42	
Castor oil, 1		Morphine and scopolamine plus rectal ether, 12	
Quinine, 3		Barbiturates alone, 2	
Clyses, 19		Barbiturates and scopolamine, 16	
Pituitary drugs, 6		Barbiturates and scopolamine plus rectal ether oil, 3	
(Dangerous!)			
<i>Vaginal examinations:</i>		<i>Rectal examinations:</i>	
None	in 4 cases	None	in 20 cases
1	in 11 cases	1	in 15 cases
2	in 12 cases	2	in 15 cases
3	in 16 cases	3	in 21 cases
4	in 18 cases	4	in 8 cases
5	in 16 cases	5	in 5 cases
Over 5	in 9 cases	6	in 2 cases
<i>Operative maneuvers during first stage</i>			
None in 71 cases; manual dilatation, 5; bag, 8; manual dilatation plus bag, 2			
<i>Operative maneuvers during second stage</i>			
Manual dilatation, 16; high forceps, 2; incisions of cervix, 2 (midpost. lip, 1; midant. lip, 1); medium "A" forceps, 18, with cervix pushed up in 8 cases.			
Note: Full dilatation and effacement awaited in 18 other cases of which 10 were delivered by medium "B" and 8 by low forceps.			

TABLE V. METHOD OF DELIVERY

Laparotrachelotomy	36	
Extraperitoneal (Latzko)	8*	
Midclassical	1	
	—	
Total cesarean sections		45
High forceps	2	
Medium forceps	28	
Mid "A"	18†	
Mid "B"	10	
Low forceps	9	
	—	
Total forceps		39
Version and extraction		1
Decomposition and breech extraction		1
		—
Total cervical dystocia cases		86

\*One of these followed attempted mid "A" forceps. Mother and baby living and well.

†Cervix pushed up during traction in 8 of these.

analgesia sufficient to induce sizable rest periods. This rest was often followed by stronger, better spaced contractions and real progress in the cervix. Dilatation and effacement seemed to be furthered, and were certainly more accurately observed by vaginal than by rectal examinations.

*First Stage.*—One of three main lines of treatment was followed: first, elective cesarean section for those patients where the cervix was so scarred, diseased, or congenitally maldeveloped as to preclude vaginal delivery with safety. Second, the

TABLE III. CHARACTER OF LABOR IN CERVICAL DYSTOCIA

<i>Stage I:</i> Average 38 hours 57 minutes; extremes 10 to 96 hours; 30 hours or more in 61 cases				
<i>Stages II and III:</i> Zero or unrecorded in cesarean sections and many operative vaginal deliveries				
<i>Total duration of labor:</i> Average 40 hours 12 minutes; extremes 10 to 96 hours; 36 hours or more in 51 cases				
<i>First stage contractions:</i> (at their best)	Strong	71 cases	Regular	59 cases
	Moderate	8 cases	Irregular	23 cases
	Weak	3 cases	Not noted	4 cases
	Not noted	4 cases		
<i>Frequency of first stage contractions: (at best)</i>				
Every 2 min. or less:	29 cases	90 seconds	56 cases	
Every 3 min. or less:	31 cases	70 seconds	2 cases	
Every 4 min. or less:	6 cases	60 seconds	6 cases	
Every 5 min. or less:	16 cases	50 seconds	15 cases	
Every 6 min. or less:	1 case	40 seconds	22 cases	
Not noted in 3 cases		30 seconds	7 cases	
		20 seconds	3 cases	
		Not noted in 30 cases	1 case	
<i>Description of the cervix:</i>				
Thick, 54; long, 11; cuff, 2; slowly or incompletely effaced, 7; firm or rigid, 33; tough, 9; leathery, 2; wiry, 1; rubbery, 2; cartilaginous, 3; thin, 3; edematous, 9; soft but thick, 14; undilatable, unyielding, 20; dilating very slowly, 34; thin parchment, 6; firm rim, 6; persistent long anterior lip, 9 (persistent posterior lip not noted); lacerated, 3; scarred, 2				
<i>Final dilatation achieved:</i>				
Fully, 19; 10 cm., 7; 9 cm., 6; 8 cm., 8; 7 cm., 5; 6 cm., 7; 5 cm., 7; 4 cm., 5; 3 cm., 7; 2 cm., 10; 1 cm. or none, 5				

Therefore vaginal examinations were indispensable and had to be repeated at fairly frequent intervals to determine progress.

#### PROPHYLAXIS

Early marriage and pregnancy, good hygiene and control of diseases of the genital organs should prevent some cases of cervical dystocia. Others can be avoided by reduction of trauma due to radical obstetrics, induced abortions, indwelling pessaries, coagulation, amputation, and tracheloplasty. Of all these, the Sturmdorf tracheloplasty gives the lowest incidence of subsequent stenosis and cervical dystocia, according to Bullard's study.<sup>1</sup>

#### MANAGEMENT

The choice was often difficult between watchful waiting and surgical intervention, between stimulation and sedation, between vaginal and rectal examinations or abstention from such examinations, between abdominal or vaginal delivery, and between the various surgical procedures. The conduct of labor is reviewed in Tables IV and V, the former concerned with the handling of the cervix, the latter giving the method of delivering the child. Individual case records yield the impression that the best results were obtained in those patients who had maintenance of fluids and nutrition, good elimination, and sedation and



While subsequent labor was easy in 13 out of 20 patients, cervical dystocia was repeated in 3 (15 per cent), and elective cesarean section in the remaining 4 was performed for fear of its repetition. Although modern chemotherapy will reduce morbidity and infection, the other maternal and fetal complications listed in Tables VI and VII indicate how serious is the choice between abdominal and vaginal delivery.

TABLE VI. MATERNAL END-RESULTS

*Deaths:* One (1.2 per cent) on tenth day after extraperitoneal cesarean section following 55-hour labor. Pelvic and wound infection, thrombosis, coronary embolism, and circulatory collapse.

*Mild uterine infection:* ("sapremia") 14

Infections of perineum or vaginal wall 6 in 41 deliveries

Abdominal wound infections, 7 in 10 cesarean sections:

Laparotrachelotomy, 2 in 36 cases

Extraperitoneal, 5 in 8 Latzkos, all drained

*Mastitis,* 3; *pyelitis,* 5, *cystitis,* 1; *bronchopneumonia,* 1; *pleurisy,* 1; *pelvic phlebitis,* 1; *saphenous phlebitis,* 2; *post-partum hemorrhage,* 1; *puerperal psychosis,* 1

*Lacerations of the cervix:*

Discovered during delivery, 20:

stellate, 2; bilateral, 7; right, 7; left, 4

Immediately repaired, 16:

stellate, 1; bilateral, 6; right, 7; left, 2

Discovered in follow-up, 26 lacerations; erosions, 3; cervicitis, 2

Untraced, 27 cases

*Subsequent confinements:* 22 in 20 patients

Easy labors, with rapid first stage, 15 in 13 patients

Repeated cervical dystocia, 3 cases

Elective repeat cesarean sections, 4

TABLE VII. FETAL END-RESULTS

*Birth weight:* Average 7 pounds 11 ounces. Only 8 babies over 9 pounds  
Extremes 5 pounds 7 ounces to 10 pounds 6 ounces

*Living,* 85; *Stillbirth,* 1, 8 pounds, macerated, cord 2 loops about neck

*Neonatal deaths,* 3, as follows:

(1) High forceps, 7 pounds 6 ounces, marked asphyxia, died in 10 hours. Cerebral hemorrhage.

This patient subsequently had 8-pound 5-ounce living baby after labor of 9 hours 11 minutes, first stage 7 hours.

(2) Medium "A" forceps, 8 pounds 14 ounces, heart beat 15 minutes. Autopsy revealed lacerated falx and tentorium, and subdural hemorrhage.

(3) Medium "A" forceps, 7 pounds 2 ounces, marked molding and asphyxia. Autopsy revealed no hemorrhage or syphilis. Pathologic diagnosis was mature infant; status thymolympathicus; atelectasis.

Asphyxia, 5; marked molding, 3; birth palsy, 1; cephalhematoma, 1.

*Feeding of 82 surviving infants:* Breast, 36; bottle, 44; not noted, 2.

#### SUMMARY AND CONCLUSIONS

1. True cervical dystocia was found in only 86, or 1 per cent of 8,213 confinements at or near full term. Its incidence rose to 13.4 per cent of prolonged labors; it was the major indication for cesarean section in 9.5 per cent, for medium forceps in 3.6 per cent, and for low forceps in 1.7 per cent of such operations.

expectant treatment was tried in all patients where serious medical complications could be excluded. Development of tonic uterus, contraction ring, or maternal or fetal exhaustion led to intervention. Otherwise the labor was allowed up to full dilatation under adequate sedation and analgesia, which seemed to reduce spasm of the lower uterine segment and cervix. Best results were obtained by morphine and scopolamine and by rectal ether-oil mixtures, with or without the aid of barbiturates.

Third, when progress was unsatisfactory under expectant treatment, various operations were used to expedite cervical dilatation and effacement (Table IV). In the first stage of labor, the Voorhees' bag was used in 8 patients, manual dilatation in 5, and the two in conjunction in 2 cases, with more or less benefit. Elder clinicians such as Painter and W. A. Morgan did not hesitate to manually dilate while examining the cervix.

It was sometimes impossible to determine failure of the above measures in time to perform the ordinary types of cesarean or vaginal delivery with safety to mother and baby. It is here that the extraperitoneal cesarean section played an important role in two ways: by permitting longer test of labor and hence more vaginal deliveries; and by salvaging the misjudged case with the results noted below.

*Second Stage.*—Before vaginal delivery, various maneuvers were used to overcome the resistance of the cervix. Manual dilatation by the Harris method or by digital stretching over the presenting part was done in 16 of the 41 patients delivered per vaginam. In the so-called medium "A" forceps, applied *inside* the cervix, dilatation was gradually wrought by the head plus the blades, aided by pushing the cervix up over the head while the latter was immobilized by gentlest traction. DeLee<sup>8</sup> has truly said that most so-called manual and instrumental dilatations are in reality incisions or tears made with a blunt instrument. It does not follow that Dührssen's incisions are preferable. The tension made by the forceps, or head in the forceps, or by the fingers pushing the cervix over the immobilized head is distributed over the *entire circumference* of the cervix up to the limit of its endurance. Thus lacerations are obviated or minimized; if Dührssen's incisions have to be added, their extension is less likely. In the 18 medium "A" forceps cases noted in Table IV, incisions of the cervix were not performed and post-partum repairs of the cervix were either shortened or entirely unnecessary.

*Third Stage.*—Examination for and repair of damage is important and here palpation is inadequate. Table VI shows many lacerations discovered only at follow-up visits. Inspection under good light with suitable retractors reveals injuries, permits immediate repair, corrects or rules out one cause of post-partum hemorrhage, reduces the area for entry of infectious organisms, and increases our knowledge of cervical dystocia and the best method for its management.

#### PROGNOSIS

End-results listed in Table VI give a maternal mortality of 1.2 per cent in 86 cases, 2.2 per cent among cesarean sections and none in 41 vaginal deliveries. On the other hand (Table VII) 1 stillbirth and 3 neonatal deaths, all following difficult forceps operations, give a fetal mortality of 4.7 per cent for the entire series and 10.3 per cent in 39 forceps deliveries. The extraperitoneal cesarean section, despite employment in relatively unfavorable circumstances, was successful in 7 out of 8 cases. With more widespread use, its mortality is decreasing as seen in the following reports:

1930 Steele <sup>2</sup>	5.5% in 59 cases
1930 Nürnberger <sup>3</sup>	5.0% in 60 cases
1932 Sackett <sup>4</sup>	7.8% in 51 cases
1937 Aldridge <sup>5</sup>	3.7% in 27 cases
1937 Norton <sup>6</sup>	1.7% in 58 cases
1939 Barrett <sup>7</sup>	2.9% in 34 cases

## REFERENCES

- (1) *Bullard, E. A.*: AM. J. OBST. & GYNEC. 27: 668, 1934. (2) *Steele, K. B.*: Ibid. 19: 747, 1930. (3) *Nürnbergger, L.*: Arch. f. Gynäk. 142: 106, 1930. (4) *Sackett, N. B.*: Bull. Lying-in Hosp., New York, February, 1932. (5) *Aldridge, A. H.*: AM. J. OBST. & GYNEC. 33: 788, 1937. (6) *Norton, J. F.*: Ibid. 33: 800, 1937. (7) *Barrett, R. L.*: Ibid. 37: 434, 1939. (8) *DeLee, J. B.*: Principles and Practice of Obstetrics, ed. 6, Philadelphia, 1933, W. B. Saunders Co., p. 990.

120 EAST SEVENTY-FIFTH STREET

## PROPHYLACTIC EXTERNAL CEPHALIC VERSION\*

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THE incidence of breech presentation has been shown to be between 2.3 and 4 per cent.<sup>1, 7</sup> The fetal mortality from breech delivery varies in reported series<sup>1-3, 8-11</sup> from 6.9 to 25 per cent. When this figure is compared with a fetal mortality (excluding abortions and nonviable fetuses) of 4.1 per cent, which was reported by the Boston Lying-in Hospital for 1939,<sup>12</sup> it is at once apparent that any procedure which reduces the incidence of breech presentations is worth while. For this reason the maneuver of external cephalic version was instituted as a routine procedure for all breech presentations from the twenty-eighth week of pregnancy to term in the prenatal clinics of the Boston Lying-in Hospital for a period of four years.

Randall<sup>13</sup> reports this maneuver was mentioned by Hippocrates and practiced by the ancients. Bartholomew<sup>14</sup> reviewed briefly the history of version and states that Wiegand in 1807 revived the practice but limited it to oblique and transverse presentations only, whereas Mattei first extended the indication to breech presentations, and to Pinard belongs the credit of popularizing the operation. In recent years Ryder,<sup>8</sup> Siegel and McNally,<sup>15</sup> Cannell and Dodek,<sup>11</sup> Mehta,<sup>4</sup> Bartholomew,<sup>14</sup> Glassman,<sup>16</sup> and many others enthusiastically endorse its routine employment and report between 75 and 90 per cent success.

At the Boston Lying-in Hospital during the years in which the study was made, an average of 3,487 patients were delivered each year in the hospital and in the out-patient department, so that in all, 13,948 were seen.

The procedure followed was palpation of each case at the twenty-eighth, thirty-second, and thirty-sixth week of pregnancy. If a breech were detected, version was attempted and the case was then followed at weekly intervals until the vertex presentation had persisted for three weeks. If the breech presentation recurred or version was unsuccessful additional attempts were made. Anesthesia was employed in selected cases, such as in primiparas with contracted pelvis and when it was felt that the resistance of the skeletal musculature was the factor in making the version difficult.

Although several obstetric textbooks describe the maneuver in this series, no set procedures were carried out. The patient's bladder was

\*Read at a meeting of the Obstetrical Society of Boston, March 18, 1941.

2. A review of possible etiologic factors points to the occurrence of cervical dystocia in two types of patients: first the elderly primigravida with menstrual and marital history, general habitus and local findings suggestive of constitutional deficiency and genital underdevelopment. In 78 patients this was the first full-term pregnancy, and of the 8 multiparas 4 had had previous cervical dystocia.

The second type presents history and objective evidence of trauma or disease affecting the cervix. Its abnormal condition or behavior is discovered ante partum (Table II) or intrapartum (Table III), and often confirmed in subsequent confinements by repetition of cervical dystocia in at least 15 per cent. This high incidence compares with 1 per cent among full-term confinements in general.

3. The clinical picture of cervical dystocia is characteristic, as shown by the labor records of 86 cases. In reaching a decision as to diagnosis and treatment, vaginal examinations at reasonably frequent intervals are indispensable. Where the cervix is stationary, despite strong contractions, it is better to intervene before local congestion and edema, maternal or fetal distress make the outlook unfavorable.

4. It follows that vaginal delivery in cervical dystocia often involves application of the forceps blades to the head inside a cuff of cervix. Such cases are designated medium "A" forceps to distinguish them from medium "B" forceps in which the cervix has retracted out of the way. This classification leads to more accurate diagnosis and comparison of different methods of treatment.

5. In 41 vaginal deliveries, the cervix was incised only twice, and not at all in 18 medium "A" forceps operations. Combined digital and forceps dilatation usually obviates these incisions; and if they have to be added, their extension is less likely.

6. In the period of 1930 to 1935, inclusive, the employment of cesarean section for cervical dystocia has increased, while the use of forceps has decreased, and for two reasons: First, the condition has been recognized and feared and laparotrachelotomy performed *earlier* in labor. Second, where the decision was made *late* in labor and in cases where transperitoneal operation would be hazardous, the extraperitoneal cesarean section has been increasingly used in place of forceps or craniotomy.

7. The extraperitoneal cesarean section by the method of Latzko, despite its use under relatively unfavorable circumstances in 8 cases, had a favorable outcome for all babies and all but one mother. Citations from the literature indicate that with more widespread use its results have improved. Of equal importance is the possibility of its employment late in labor, which permits a longer test of labor and, hence, more deliveries per vaginam.

8. Maternal and fetal mortality, morbidity, and complications are more frequent in cervical dystocia than in average labors; and the operative incidence is much higher. In view of this a plea is made for more conservatism in the medical and surgical treatment of injuries and disease of the female genital tract in the childbearing age.

I gratefully acknowledge many helpful suggestions by Dr. C. F. Jellinghaus and Dr. Albert H. Aldridge in the preparation of this report.

This figure is explained by the fact that extra attempts at version were necessary when the breech recurred and when the initial attempts were unsuccessful. Version was successful in 829 cases, or 72 per cent. At term only 20.8 per cent of the primiparas and 6.4 per cent of the multiparas presented breeches (50 per cent and 35 per cent, respectively). Recurrence to breech presentation occurred in 224 of the successful versions, or 27 per cent. Spontaneous version occurred 108 times, or 19.35 per cent, in those cases in which attempted version was unsuccessful or in which recurrence of a breech presentation occurred.

These figures are shown in Fig. 1.

It may be seen that the greatest number of successful versions were performed in the thirty-second week. The successful and the unsuccessful attempts roughly parallel each other in a ratio of about 3 to 1 until the thirty-fourth week after which, as term is approached, they come together. This would be expected for version becomes more difficult as the fetus increases in size, the uterus becomes more spastic and the abdominal wall more tense, all of which occur as term is approached. The recurrence of breech presentations and spontaneous versions also roughly parallel each other with the maximum number of each occurring at the thirty-fourth week and a ratio of about 2 to 1 holding throughout.

The presentation at the onset of labor for the 793 cases is shown in Table I. Of the vertex presentations, the figures shown in Table II obtained as to position. Table III demonstrates the manner in which these 793 patients were delivered.

TABLE I

	PRIMIPARA		MULTIPARA		TOTAL	
	NO.	%	NO.	%	NO.	%
Vertex	190	78.8	518	94.0	709	89.5
Breech	42	20.3	31	5.6	80	10.1
Transverse	1	0.4	2	0.4	3	0.3
Face	1	0.4	0	0.0	1	0.1
Total	241		552		793	

TABLE II

	L.O.A.	L.O.T.	L.O.P.	R.O.A.	R.O.T.	R.O.P.
No.	159	34	49	100	26	48
%	38.2	8.2	11.7	24.0	6.2	11.0

TABLE III

	PRIMIPARA		MULTIPARA		TOTAL	
	NO.	%	NO.	%	NO.	%
Normal	107	44.4	492	89.1	599	75.7
Low forceps	78	32.3	12	2.4	90	11.3
Breech	42	17.4	31	5.6	73	9.2
Section	14	5.8	11	2.0	25	3.1
I.P.V. and Braxton Hicks	0	0	6	0.9	6	0.7
Total	241		552		793	

As may be seen in Table III, 25 patients, or 3.1 per cent, were delivered by cesarean section. Of this number the indication for 7 was primiparous breech with pelvic contracture, 1 transverse presentation in a primipara, and for 1 face presentation in a primipara. The indication in the remaining 16 cases was about equally divided between bleeding and cephalopelvic disproportion. It is interesting

emptied and, if possible, the rectum. Lifting the breech well up from the pelvis and moving it to one side or the other before bringing the head down was found to be essential. If possible, the baby was rotated so that the flexion was preserved, but if there was less resistance, rotation in the opposite direction was used. Elevation of the foot of the table as first suggested by Fröhnholtz<sup>17</sup> in 1904 to an angle of 45 degrees is helpful to disengage the breech from the pelvis. In some cases it was necessary to push the breech up by a finger inserted in the rectum. No pads or bindings were employed to maintain the vertex presentation once it had been established.

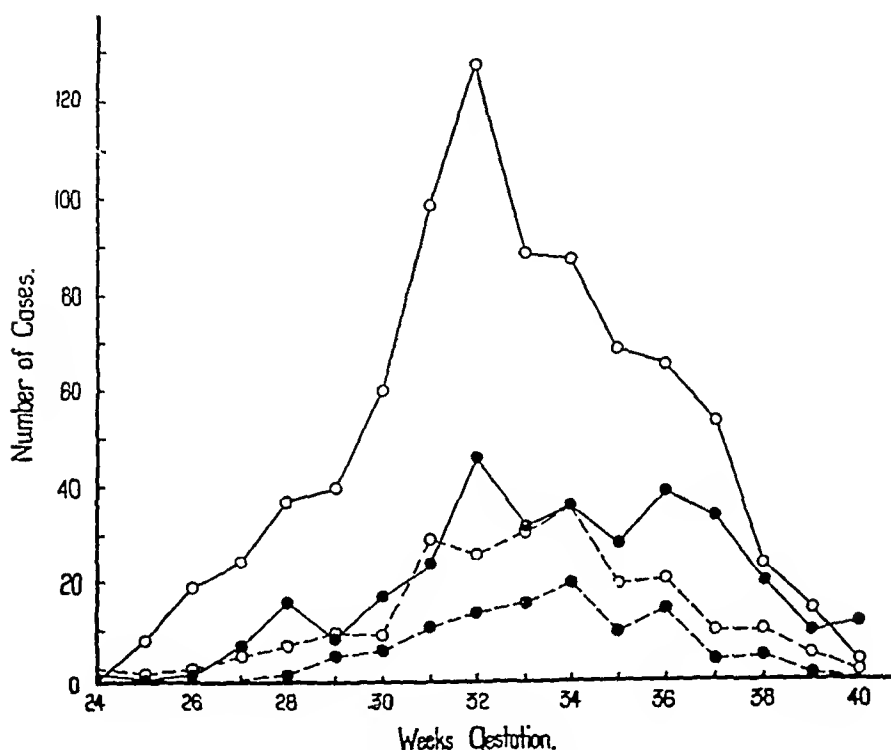


Fig. 1.—Results of external cephalic versions. ○-○, Successful versions; ●-●, unsuccessful versions; ○-●-○, recurrent breech presentations; ●---●, spontaneous versions.

In general, it may be said that external cephalic version is indicated in all cases during the last trimester of pregnancy, unless any of the following conditions exists:

1. Multiple pregnancy.
2. History of vaginal bleeding.
3. History of previous myomectomy and abdominal hysterotomy.
4. Marked deformities of the fetus, such as hydrocephalus and anencephalus.
5. Marked pelvic contraction.

In slight and moderate degrees of pelvic contraction, a vertex presentation is of great value as it permits the patient a test of labor.

The diagnosis of breech presentation was made in 793 cases in a total of 13,948 patients, or 5.6 per cent, from the twenty-fourth week of pregnancy to term. Of this number 241, or 30.4 per cent, were primiparas. A total of 1,161 versions were attempted, or 1.46 versions per case.

Anesthesia has been employed by various men but, for the most part, has not been enthusiastically indorsed. In fact, many of the serious complications reported have resulted from the use of too much force while the patient was under an anesthetic.

In this series, anesthesia was used in selected cases when a vertex presentation was particularly desirable and when it was felt that lack of cooperation in securing relaxation of the abdominal muscles could best be circumvented by this method. In all, anesthesia was employed 48 times, of which 18 versions were successful. Inhalation of nitrous oxide, oxygen, and ether was used in 12 cases, while intravenous administration of evipal or pentothal was used in the other 36. The latter type was more satisfactory, as it required no preliminary medication and the patients were ambulatory in a much shorter time.

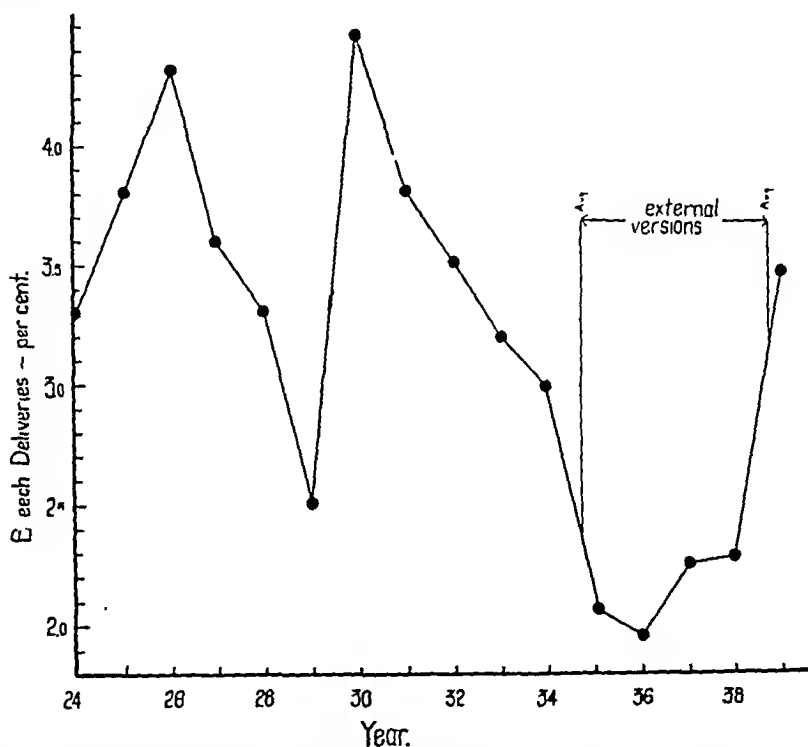


Fig. 2.—Incidence of breech deliveries, 1924-1939. Percentage of total deliveries plotted chronologically. The period, August, 1934 to August, 1938, when external versions were routine is indicated.

As so little is known concerning the reason for breech presentation, it was thought of interest to tabulate the cases of patients in whom any cause could be determined as well as the cases of patients who had previously been delivered of breech presentations. There were only 17 of the latter, or 2.2 per cent. In 54 patients, or 6 per cent, some cause for the breech presentation was found (Table V).

During the four-year period of this study, there were 246 breech deliveries out of a total of 10,529 hospital deliveries, or an incidence of 2.33 per cent. This figure compares favorably with the breech incidence of 3.75 per cent for the four-year period prior to the routine adoption of external cephalic version. (Fig. 2.)

There is no doubt that the incidence of 2.33 per cent could be lowered when the fact emerges that of 246 breech deliveries which occurred, in

to note that DeNormandie<sup>18</sup> found an increase in the incidence of sections with the indication of primiparous breech in his survey of cesarean sections in Massachusetts in 1939. The maternal mortality was zero, no patients having died because of this manipulation or from any other cause. The gross fetal mortality including macerated, stillborn, and neonatal deaths for this series was 32, or 4.03 per cent, which compares favorably with the gross fetal mortality of the Boston Lying-in Hospital.<sup>12</sup> Table IV shows the distribution of the deaths.

TABLE IV

Term	STILLBIRTHS		NEONATAL DEATHS	
	DELIVERY	NUMBER	DELIVERY	NUMBER
	VVVVV*	10	VVVVV	6
Premature	BBBBB		B	
	VVVVV	7		0
	TT			
Congenital anomalies	VVVV	5	VVV	4
	B		F	
Total		22		10

\*V, Vertex; B, breech; T, twin; F, face.

Subtracting the 9 cases where the cause of death was gross fetal anomalies, the corrected mortality was 23, or 2.9 per cent. Two of these deaths were accounted for by separation of the placenta ten days following an attempt at version with a twin pregnancy. In 6 cases, death followed breech extraction where version had been unsuccessful.

The most frequent complications resulting from version, mentioned in the literature, are fetal death due to some interference with the circulation of the cord or some degree of separation of the placenta. McCullagh<sup>19</sup> reported 4 cases of rupture of the uterus during labor due to neglected compound presentations. In these cases antenatal version had been performed on frank breech presentation, and the legs had remained extended.

In this series the complications are considered under three headings. Those occurring because of some interference with the cord circulation; cases in which antenatal bleeding occurred; and stillbirths following version in which no cause could be determined.

The cord was found about the neck in 66 cases, or 8.3 per cent. In 2 cases, fetal distress developed during labor due to this complication, but living babies were delivered. In only 1 case did stillbirth result, the cord being tightly about the neck 2 times. Another stillbirth was attributed to a true knot in the cord. There were 4 cases in which the cord prolapsed during labor, and 2 cases in which the cord was around one or more of the extremities. Living babies were delivered in all 6 cases. In only 4 cases out of the entire series, or 0.5 per cent, was it necessary to restore the breech presentation because the fetal heart was slowed and irregular after cephalic version. Spotting in small amounts occurred in 7 cases. In 2 of these cases, the spotting appeared directly after version. In the remaining 5, the spotting appeared from one to six weeks after the version. All 7 babies were born alive. The diagnosis of separation of the placenta was made four times. In 3 cases the separation occurred nine, eight, and seven weeks, respectively, after the version, and all 3 babies were born alive. In the fourth case, version was attempted on a multiple pregnancy through mistaken diagnosis in the thirty-fifth week of pregnancy. One week later partial separation of the placenta occurred, both babies being born alive but died soon after birth.

There were 5 patients from whom macerated babies were delivered. In all of these cases there were no demonstrable causes of death. Delivery was effected at 2, 3, 6, 6, and 6 weeks, respectively, after version, and in each case the fetal heart was known to be normal one week after version.



# BLOOD CHOLINE VARIATIONS IN PREGNANCY, IN LABOR, AND IN THE PUERPERIUM

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## REVIEW OF LITERATURE

THE first extraction of a physiologically active substance from the human placenta was made in 1885 by Böhm,<sup>1</sup> who found an average of 50 mg. of choline per placenta.

Twenty-two years later Rieländer<sup>2</sup> likewise obtained approximately the same result (average 40 mg. of choline per placenta). In the same year (1907), Dixon and Taylor<sup>3</sup> reported that the placenta produces a chemical substance which develops with the ripening of that tissue, the liberation of which by the contracting uterus and vessels might induce the onset of normal labor. In 1928, Sievers<sup>4</sup> confirmed the previously reported choline content of the placenta (average 40-45 mg. per organ) and proposed the theory that the latter tissue stored choline which was transferred to the uterus by pressure on the placenta at the time of birth, thus causing the uterine contractions. Larger amounts of choline in the placenta were reported by other authors (5.0-120.0,<sup>5</sup> 61.0-92.2,<sup>6</sup> 51.5-243.0,<sup>7</sup> 54.0-163.0,<sup>8</sup> 6.0-84.0,<sup>9</sup> 0.945.0,<sup>10</sup> and 102.0-282.0<sup>11</sup>). Smyth<sup>12</sup> has recognized a water-soluble precursor of choline in the human placenta, each molecule of which contains one molecule of choline, one of phosphoric acid, and one amino linkage.

Hauptstein<sup>13</sup> concluded that if choline were to be considered responsible for the uterine contractions during labor, it must be present as the far more powerful acetic ester, acetylcholine, and noted that in 18 cases the placenta contained acetylcholine in amount varying from 74 to 459 mg. per kg. of tissue. From then on, Bischoff and others;<sup>9</sup> Chang and Wong;<sup>14</sup> Wong and Chang;<sup>15</sup> and Wen, Chang and Wong,<sup>16</sup> who found the origin of the free placental acetylcholine to be in the syncytial layer of the villus, reported the following acetylcholine values, respectively: 168-220, 15-133.3, 12.5-133.3, and 19-104 mg. per kg. of tissue. Chang<sup>17, 18</sup> reported (1935) that there is a reserve of acetylcholine in the placenta which may be liberated from its precursor in vitro, and found (1938) that there is a "free" and a "bound" fraction of acetylcholine in the human placenta. Hunt<sup>19</sup> pointed out many years ago that intravenous injection in cats of as little as 0.000,000,0024 mg. of acetylcholine per kg. body weight can cause a pronounced fall in blood pressure. The presence in the placenta of such large amounts of this powerful substance may be more than a coincidence.

That the uterus responds to choline by contraction has been known for some time, particularly since the reports of Müller,<sup>20</sup> Adler<sup>21</sup> and Berlin<sup>22</sup> who pointed out that the effect of choline on the uterus of the cat or mouse simulated the contractions in labor. Engeland and Kutscher<sup>23</sup> have reported that choline causes tetanic contractions of the gravid uterus, and Alberts<sup>24</sup> has stated that the gravid uterus is more sensitive to choline than the nongravid one. In a study of the quantitative action of acetylcholine on the guinea pig uterus, Webster<sup>25</sup> found that the height of contraction varies with the concentration, but even a molar concentration of  $4.4 \times 10^{-7}$  gave good contractions. Sherif<sup>26</sup> showed that acetylcholine acts as the chemical transmitter of the effects of the hypogastric nerves on the uterine muscle, similar to that of the vagi nerves.

The effectiveness of acetylcholine as an oxytocic agent was recently studied in a series of 28 patients.<sup>15</sup> In 7 out of 16 cases in which the membranes were intact,

TABLE V. CAUSES OF BREECH PRESENTATION

Contracted pelvis	34
Placenta previa	8
Fibromyomas of uterus	4
Congenital malformations	4
Hydramnios	2
Laxity of abdominal wall	1
Cyst of ovary	1
	54

149, or 60.5 per cent, version was not attempted. This paradox is explained when it is found that in 121 cases, or 49 per cent, the diagnosis of breech presentation was not made until the patient was admitted for delivery. This seemingly unusual figure is somewhat improved by the fact that 38 cases were either nonviable or premature babies.

A four-year study of the results of the routine employment of external cephalic version was made. A diagnosis of breech presentation was made in 793 of a total of 13,948 cases, or 5.6 per cent. A total of 1,161 versions, or 1.46 per case, were attempted, 72 per cent being successfully accomplished. The recurrence rate was 27 per cent. Spontaneous version occurred 108 times, or 19.35 per cent, in cases where either recurrence had taken place or version had been unsuccessful. Anesthesia was helpful but was employed only in selected cases. The presentation and type of delivery employed are tabulated for the 793 cases. There was no maternal mortality. The gross fetal mortality was 4.03 per cent. The breech incidence at the Boston Lying-in Hospital was reduced from 3.75 per cent to 2.33 per cent.

External cephalic version employed routinely is a safe procedure and will reduce by more than 38 per cent the incidence of breech presentation with its inevitably high fetal mortality.

## REFERENCES

- (1) Pierson, R. N.: Surg. Gynec. & Obst. 37: 802, 1923.
- (2) Studdiford, W. E.: J. A. M. A. 99: 1820, 1932.
- (3) Goethals, T. R.: Surg. Gynec. & Obst. 62: 525, 1936.
- (4) Mehta, C.: Brit. M. J. 1: 706, 1937.
- (5) Dearnley, G.: Ibid. 2: 371, 1931.
- (6) DeLee, J. B.: Principles & Practice of Obstetrics, ed. 7, Philadelphia, 1938, W. B. Saunders Co.
- (7) Stander, H. J.: Williams Obstetrics, ed. 7, New York, 1936, D. Appleton-Century Co.
- (8) Ryder, G. H.: Surg. Gynec. & Obst. 37: 660, 1923.
- (9) King, E. L., and Gladden, A. H.: AM. J. OBST. & GYNEC. 17: 78, 1929.
- (10) Gibberd, Z. F.: Brit. M. J. 2: 369, 1931.
- (11) Cannell, D. E., and Dodek, S. M.: AM. J. OBST. & GYNEC. 27: 517, 1934.
- (12) Boston Lying-in Hospital, Annual Report, 1939-1940.
- (13) Randall, L. M.: Proc. Staff Meet. Mayo Clin. 9: 5, 1934.
- (14) Bartholomew, R. A.: AM. J. OBST. & GYNEC. 14: 648, 1927.
- (15) Segel, I. A., and McNally: Ibid. 37: 86, 1939.
- (16) Glassman, O.: Ibid. 24: 277, 1932.
- (17) Decugniere (Marcel): La Version par Maneuvres externes, en Position de Trendelenburg dans les Presentations due Siege, Paris, 1923, p. 47.
- (18) DeNormandie, R. L.: New England J. Med. 223: 45, 1940.
- (19) McCullagh, W. M. H.: Brit. M. J. 2: 646, 1933.
- (20) Irving, F. C., and Goethals, T. R.: AM. J. OBST. & GYNEC. 11: 80, 1926.
- (21) Irving, F. C.: Textbook of Obstetrics, New York, 1936, The Macmillan Co.
- (22) Wrigley, A. J.: Brit. M. J. 1: 891, 1934.

or four analyses were performed on the same sample. Frequent blank determinations and control analyses were likewise performed. With but few exceptions all of the 87 experimental subjects were in good health. Some of the 18 male and 19 nonpregnant female controls were subsequently admitted to Billings Hospital from the Out-Patient Department (where the latter samples were obtained), but none was gravely ill or in acute distress at the time the blood sample was taken.

## RESULTS

*Blood Choline in Pregnancy.*—Table I records the choline values on venous blood samples taken from 62 subjects at times varying from just prior to the onset of labor to 207 days before delivery. It may be seen that from the third lunar month of pregnancy (197-224 days before delivery) to term there was no significant variation in the average choline values, which for the third to the tenth lunar month inclusive were 13.3, 13.1, 14.9, 13.9, 12.9, 12.2, 13.1, and 13.1 mg. per liter, respectively. The average choline results for 28 primigravidas, 14 secundigravidas, and 20 multiparas were, respectively, 13.3, 12.4, and 13.2 mg. per liter; the grand average for all 62 subjects was 13.1 mg. of choline per liter of blood.

*Blood Choline During Labor and Post Partum.*—Table II summarizes the data on 17 subjects in various stages of labor. The average choline value for the entire group was 15.0 mg. per liter, somewhat higher than that for blood during pregnancy. Table III shows the post-partum choline results on 8 subjects. In 6 cases in which

TABLE II. BLOOD CHOLINE VALUES IN LABOR

NO.	AGE YEARS	OB- STET. HIS- TORY <sup>a</sup>	TIME SAMPLE HR.-MIN.	DURATION OF LABOR				DUR. OF PREG. WK.	BABY		CHO- LINE FOUND MG./ LITER	DE- LIV- ERY
				STAGES			TOTAL HR.- MIN.		WT. GM.	SEX		
				1ST HR.- MIN.	2ND HR.- MIN.	3RD HR.- MIN.						
63	26	1,0,1,0	6-10 <sup>b</sup>				24-30	40	e	M	13.5	c
64	24	0,0,0,0	6-11 <sup>b</sup>	13-45	0-51	0-7	14-43	39	3630	M	18.2	f
65	18	0,0,0,0	7- 0 <sup>b</sup>	18-40	1-15	0-3	19-58	40	4150	F	13.6	g
66	23	2,0,0,2	7- 0 <sup>b</sup>	9-35	0-10	0-15	10- 0	40	2800	F	12.8	h
67	30	0,0,0,0	7-10 <sup>b</sup>	15- 0	1-17	0- 8	16-25	40	3025	M	21.2	i
68	20	0,0,0,0	7-30 <sup>b</sup>	14-35	1-16	0-9	16- 0	40	3255	F	11.7	j
69	20	0,0,0,0	8-17 <sup>b</sup>	14-50	1-53	0- 8	16-51	40	3590	F	18.3	j
70	28	3,0,0,2	8-55 <sup>b</sup>	11- 5	0-22	0- 8	11-35	40	3265	F	14.3	h
71	19	0,0,0,0	9- 0 <sup>b</sup>	29- 0	1-35	0-12	29-47	40	3360	M	12.4	g
72	34	3,0,0,3	9- 3 <sup>b</sup>	11-30	0-31	0-10	12-11	40	4570	M	14.1	h
73	40	5,0,2,3	11- 8 <sup>b</sup>	11-15	0-11	0- 4	11-30	40	3840	M	13.7	h
74	28	0,0,0,0	11-43 <sup>b</sup>	27-15	1- 8	0- 7	28-30	40	3375	M	22.8	g
75	23	0,0,0,0	19-35 <sup>b</sup>	23-55	0-29	0- 6	24-30	40	3245	M	10.7	j
76	27	1,0,0,1	25-58 <sup>b</sup>	41- 0	0- 6	0- 4	41-10	41	3955	M	12.2	k
77	27	2,0,1,1	Onset <sup>c</sup>	18-30	0-58	0- 6	19-44	40	3175	F	15.0	j
78	16	0,0,0,0	<sup>d</sup>	20-55	1-25	0- 2	22-22	38	3460	F	11.9	l
79	25	2,0,2,0	End <sup>e</sup>	7-15	0-37	0- 5	7-58	40	3230	F	19.3	g

<sup>a</sup>Previous pregnancies, premature labors, abortions, children now living.

<sup>b</sup>After onset of first stage of labor.

<sup>c</sup>Second stage of labor.

<sup>d</sup>Seven minutes after onset of second stage of labor.

<sup>e</sup>Twins: I, midforceps, 2,390 Gm., M.; II, breech extraction, 2,375 Gm., M. Acute fulminating toxemia; five convulsions during delivery; placenta removed manually.

<sup>f</sup>Forceps rotation; low forceps with episiotomy.

<sup>g</sup>Spontaneous delivery with episiotomy.

<sup>h</sup>Spontaneous delivery.

<sup>i</sup>Mild toxemia; spontaneous delivery with episiotomy.

<sup>j</sup>Low forceps with episiotomy.

<sup>k</sup>Midforceps with episiotomy.

<sup>l</sup>Manual rotation; low forceps with episiotomy.

acetylcholine induced labor and brought about delivery; in the other 9 cases uterine contractions were obtained but did not last long enough to terminate pregnancy. The procedure was successful in inducing labor in all of the 12 cases where the membranes were ruptured spontaneously or artificially, and rhythmic uterine contractions were initiated within a few minutes regardless of whether the patient was a primipara or a multipara.<sup>15</sup> Contractions of the guinea pig uterus after application of blood from women in labor had been noted by Brdiczka<sup>27</sup> and Fontes,<sup>28</sup> and within recent years considerable attention has been directed to the presence of some oxytocic material in the blood of women in labor.

Prior to 1923 most investigators were unable to find free choline in the blood or serum of man or animals. From 1923 to the present the values reported were zero in six instances and in twenty-four others the amounts have ranged from 0.5 to 310.0 mg. per liter. The lowest values on human blood (aside from zero) were obtained by Kahlson<sup>29</sup> (2.2-8.5 mg./liter), and the highest by Vasiliu<sup>30</sup> (18.2-147.0 mg./liter). The inaccuracy and nonspecificity of the methods employed can account for such wide divergence in results. Some of these methods are discussed in connection with a study of the choline content of biologic fluids.<sup>31</sup>

## METHOD

The method used in the present study has been described in detail elsewhere.<sup>31</sup> Blood choline determinations were made on venous (arm) blood of women in various stages of pregnancy, labor, and the puerperium at the Chicago Lying-in Hospital or its "Stockyards Dispensary." The analyses were done in duplicate; in some cases even three

TABLE I. BLOOD CHOLINE VALUES DURING PREGNANCY

NO.	AGE YEARS	OBSTET. HISTORY*	DAYS BE- FORE DE- LIVERY	CHOLINE FOUND MG./LITER	NO.	AGE YEARS	OBSTET. HISTORY*	DAYS BE- FORE DE- LIVERY	CHOLINE FOUND MG./LITER
1	22	0,0,0,0	0	12.1	32	27	0,0,0,0	40	15.2
2	19	0,0,0,0	1	15.8	33	23	0,0,0,0	41	11.6
3	22	0,0,0,0	1	10.9	34	43	1,0,0,1	41	13.2
4	26	0,0,0,0	1	15.6	35	31	2,0,0,2	54	13.0
5	24	3,0,3,0	3	10.4	36	34	0,0,0,0	55	11.4
6	25	1,0,0,1	4	10.0	37	29	2,0,0,2	55	16.2
7	18	1,0,1,0	4	13.2	38	32	6,0,2,4	61	11.5
8	27	1,0,0,1	5	12.6	39	19	1,0,0,1	61	13.6
9	21	1,0,0,1	7	12.8	40	35	4,0,2,2	62	12.0
10	24	0,0,0,0	7	12.1	41	28	1,0,0,1	66	12.7
11	18	0,0,0,0	9	12.4	42	29	5,0,0,5	67	11.3
12	28	3,0,0,3	9	14.4	43	25	0,0,0,0	68	10.6
13	23	2,0,0,3	10	12.6	44	24	2,0,0,2	72	14.6
14	22	0,0,0,0	10	11.2	45	18	0,0,0,0	79	13.8
15	23	2,0,0,1	11	11.9	46	41	11,0,0,11	83	9.9
16	28	0,0,0,0	11	19.0	47	23	2,0,0,2	85	13.7
17	30	1,0,0,1	12	12.8	48	27	0,0,0,0	90	12.3
18	21	0,0,0,0	16	15.0	49	19	0,0,0,0	91	10.2
19	38	2,0,0,2	16	13.6	50	31	1,0,0,1	94	10.6
20	23	0,0,0,0	17	14.4	51	35	5,0,0,5	98	19.9
21	26	0,0,0,0	20	12.9	52	21	1,0,0,1	100	10.6
22	27	0,0,0,0	21	12.0	53	24	1,0,0,1	114	11.1
23	19	1,0,0,1	23	13.3	54	31	2,0,0,2	120	14.4
24	23	0,0,0,0	24	12.9	55	22	0,0,0,0	125	16.3
25	31	6,0,0,6	25	11.2	56	22	1,0,0,1	145	14.0
26	21	0,0,0,0	26	15.0	57	21	2,0,0,1	150	15.8
27	23	0,0,0,0	26	11.4	58	27	3,0,0,3	172	12.0
28	27	0,0,0,0	28	16.4	59	23	3,0,1,2	176	12.8
29	28	0,0,0,0	32	11.6	60	24	6,0,5,1	178	13.1
30	23	0,0,0,0	32	11.8	61	22	0,0,0,0	179	14.5
31	27	0,0,0,0	37	14.1	62	22	1,0,0,1	207	13.3

\*Previous pregnancies, premature labors, abortions, and children now living.

In a study of the choline content of the saliva during the menstrual cycle, Eagle<sup>31</sup> found that the choline value showed a cyclic variation, the maximum deviations from the lowest level for each of four subjects being 396, 294, 226, and 398 per cent, respectively. The choline curves showed peaks occurring on the second to seventh day, on the thirteenth to sixteenth day, and on the twenty-second to twenty-fourth day of the cycle, all of which are periods of considerable uterine activity. The results in the present study likewise indicate an elevated choline content of the blood (immediately following the delivery of the placenta) at a period of great uterine activity.

It will be recalled that choline and acetylcholine are normal constituents of the body; that the latter, which is recognized as the chemical transmitter of the effects of the hypogastric nerve on uterine muscle, is a powerful oxytocic agent causing rhythmical contractions of the uterus in man and animals; that the gravid uterus is more sensitive to choline and acetylcholine than the nongravid one; that the acetylcholine content of the uterus may be increased by estrin injection; and that the choline content of the blood and saliva is markedly elevated during periods of great uterine activity. On the basis of the foregoing, it is concluded that, whatever be the cause or causes of the onset of labor, the possible role of choline and its powerful esters in facilitating the emptying of the uterus at term should be considered.

#### SUMMARY

1. Choline determinations were made on blood samples from 62 women in various stages of pregnancy, 17 women in labor, 8 women in the puerperium, 19 nonpregnant females, and 18 males, a total of 124 samples.

2. The choline content of the blood from pregnant women is fairly constant from 207 days before delivery to term (average 13.1 mg./liter).

3. The blood choline value is slightly increased during labor (average 15.0 mg./liter).

4. The choline level is highest just after delivery (average 24.6 mg./liter). In two cases which were 44 and 48 days post partum, the choline results were 13.4 and 11.3 mg. per liter.

5. An average of 14.6 mg./liter was obtained for the choline content of blood from nonpregnant female patients; that for male patients was 13.4 mg. per liter.

I desire to acknowledge the cooperation of Dr. A. J. Carlson, and of Dr. Fred L. Adair and the Staff of the Chicago Lying-in Hospital.

#### REFERENCES

- (1) Böhm, R.: Arch. f. exper. Path. u. Pharmacol. 19: 87, 1885.
- (2) Rieländer, A.: Zentralbl. f. Gynäk. 31: 1082, 1907.
- (3) Dixon, W. E., and Taylor, F. E.: Lancet 2: 1158, 1907.
- (4) Sievers, H.: Ztschr. f. Biol. 87: 319, 1928; 88: 145, 1928.
- (5) Decio, C.: Ann. di ostet. e ginec. 37: 81, 1915.
- (6) Kottlors, E.: Zentralbl. f. Gynäk. 53: 2987, 1929.
- (7) Wrede, F., Strack, E., and Bornhofen, E.: Ztschr. f. physiol. Chem. 183: 123, 1929.
- (8) Strack, E., and Loeschke, A.: Ztschr. f. physiol. Chem. 194: 269, 1931.
- (9) Bischoff, C., Grab, W., and Kapfhammer, J.: Ztschr. f. physiol. Chem. 207: 57, 1932.
- (10) Cattaneo, L.: Arch. internat. de

TABLE III.—POST-PARTUM CHOLINE VALUES

NO.	AGE YEARS	OBSTET. HIS- TORY <sup>a</sup>	SAMPLE: TIME AFTER DELIV- ERY HR.-MIN.	DURATION OF LABOR				DUR. OF PREG. WK.	BABY		CHO- LINE FOUND MG./ LITER	DE- LIV- ERY
				STAGES			TOTAL HR.- MIN.		WT. GRAMS	SEX		
				1ST HR.- MIN.	2ND. HR.- MIN.	3RD HR.- MIN.						
80	25	2,0,2,0	0-10	7-15	0-37	0-6	7-58	40	3230	F	24.9	b
81	18	0,0,0,0	0-10	33-35	1-35	0-13	34-10	40	2970	F	22.9	b
82	21	0,0,0,0	1-16	7-30	0-34	0-21	8-25	41	3095	M	19.0	b
83	18	0,0,0,0	1-17	5-0	1-51	0-2	6-53	40	2575	F	30.7	c
84	33	1,0,1,0	2-10	38-53	1-20	0-8	40-21	36	3040	F	25.9	e
85	34	10,0,0,10	4-15	8-15	0-14	0-7	8-36	41	3520	F	24.0	f
86	27	5,0,0,5	44 days	----	----	----	2-10	40	3859	M	13.4	d
87	33	6,0,0,5	48 days	----	----	----	6-0	40	4545	F	11.3	f

<sup>a</sup>Previous pregnancies, premature labors, abortions, children now living.

<sup>b</sup>Spontaneous delivery with episiotomy.

<sup>c</sup>Manual rotation; spontaneous delivery with episiotomy.

<sup>d</sup>Unattended labor.

<sup>e</sup>Midforceps with episiotomy.

<sup>f</sup>Spontaneous delivery.

blood was taken within 255 minutes after delivery, the average choline content was 24.6 mg. per liter. The significance of this marked rise in the choline content of maternal (venous) blood immediately after delivery of the placenta is not fully understood, and its explanation must await further knowledge of the role in the organism of choline and its esters which already enjoy unique distinction as a hormone and an essential food factor. Two subjects who were forty-four and forty-eight days post partum showed low or normal blood choline values (13.4 and 11.3 mg./liter).

The average choline content of the venous blood of 18 male subjects was 13.4 mg. per liter; that for 19 nonpregnant female subjects was 14.6 mg. per liter. The ages and diagnoses on these 37 individuals varied widely.

Neither in pregnancy, in labor, nor in the puerperium was there any obvious correlation between the choline content of the blood and the previous obstetric history, the age of the mother, the total duration of pregnancy, the duration of the various stages of labor, the weight or sex of the child, the weight of the placenta or the manner of delivery.

#### COMMENT

In 1932 Jeffcoate<sup>32</sup> proposed the theory that estrin is essential for parturition, an idea which has been supported by the observations that estrin causes contractions of uterine muscle,<sup>33-35</sup> and that estrin is present in considerable quantity during pregnancy, reaching its peak at the time of parturition.<sup>36</sup> Witherspoon<sup>37</sup> suggested that an inhibitory action on estrin (by the luteinizing factor in the ovary, placenta and anterior lobe of the hypophysis) which is present during early pregnancy is released toward the end of gestation, and an increased sensitivity of the uterus to pituitrin produces uterine contractions until delivery occurs. A theory involving the excitatory action of some hormone on the numerous ganglia of the uterus leading to contraction of that organ was advanced by Gibbons<sup>38</sup> who indicated that there remained only the discovery of something sufficiently powerful to excite the uterine ganglia to produce these essential contractions. The recent observation that the acetylcholine content of the uterus significantly increased within an hour after injection of estrin and completely disappeared after twelve hours is of interest in this connection.<sup>39</sup>

## EXPERIMENTAL

Menstrual fluid was collected during the night into a clean dry Ramses spring type pessary for from six to eight hours. All subjects studied were normally menstruating, healthy females. Fourteen experiments were performed on 9 subjects in from one to two hours after collection of the menstrual fluid. When the same subject was studied on more than one occasion, the menstrual fluid was collected during different menstrual cycles. Occasionally the fluid became layered, in which instances the superficial layers were employed.

Fibrinogen was prepared by a modification of the method of Smith, Warner and Brinkhaus,<sup>18, 19</sup> in that, aside from dialysis, the preparation was made at room temperature. All reagents used were stored in the ice box. The plasma utilized was obtained from a human blood bank and contained 50 ml. of 2½ per cent sodium citrate to 500 ml. of blood. The plasma was centrifuged for thirty minutes at 2,500 r.p.m. until all the red blood cells were removed. To each 100 ml. of plasma, 10 ml. of colloidal magnesium hydroxide were added with constant stirring. After standing for ten minutes, the plasma was centrifuged at 2,500 r.p.m. for twenty minutes. In this manner the plasma was made prothrombin free. To the plasma was now added approximately one-fourth volume of saturated ammonium sulphate to produce a heavy flocculation and clumping of the fibrinogen. Occasionally, an additional 2 to 3 ml. of ammonium sulphate were found necessary. The mixture was centrifuged and the precipitated fibrinogen was redissolved in a volume of oxalated saline equal to that of the original plasma volume. The fibrinogen was again precipitated with one-fourth the original plasma volume of saturated ammonium sulphate. If the amount of precipitate seemed scanty, 3 to 5 ml. of additional ammonium sulphate were added. After centrifuging, the fibrinogen was dissolved in one-tenth the original plasma volume of oxalated saline, and dialyzed in the ice box against frequently changed oxalated saline, until the dialyzing solution gave no test for  $\text{SO}_4$  ions with  $\text{BaCl}_2$ . The final yield of fibrinogen was then stored in the ice box in 2 ml. portions. More recently, 1 ml. portions were lyophilized as suggested by Ferguson.<sup>20</sup> Such a preparation of fibrinogen is still active after two to three months.

Thromboplastin, prepared by a modification of the method of Quick<sup>21</sup> was employed in all these experiments. Activated serum was used as the thrombin solution. In order to minimize the effect of antithrombin, fresh thrombin, in the form of activated serum, was used for each phase of the experiment. To prepare this activated serum, one part of 0.28 per cent  $\text{CaCl}_2$  was added to a mixture of one part of Quick's thromboplastic solution and one part of fresh oxalated plasma. The latter was prepared by mixing 1 c.c. of 1.34 per cent sodium oxalate with 9 c.c. of blood in a 10 by 75 mm. test tube. The clot which formed in fifteen to twenty-five seconds was rolled out, and the serum used immediately.

In each experiment, the menstrual fluid was tested for the presence of thrombin, fibrinogen, prothrombin, and anticoagulants. The experiments were carried out in a 10 by 75 mm. test tube and maintained at 37.5° C. in a water bath. In each experiment, the fibrinogen was tested for the presence of prothrombin by the addition of equal quantities of thromboplastic solution and calcium. Only solutions which contained no prothrombin, or minute traces of prothrombin, were used. All experiments were carried out in duplicate.

To test for thrombin, fibrinogen was added, since that should cause the coagulation of menstrual fluid in the presence of thrombin. To 0.1 ml. of menstrual fluid was added 0.1 ml. of fresh fibrinogen solution. Incubation at 37.5° C. for sixteen to eighteen hours did not produce coagulation in any instance.

To test for fibrinogen, menstrual fluid was tested with freshly prepared thrombin, since in the presence of fibrinogen this procedure should produce a coagulation of the menstrual blood. To 0.1 ml. of menstrual blood was added 0.1 ml. of freshly

physiol. 37: 58, 1933. (11) *Strack, E., Giessendörfer, H., and Neubaur, E.*: Ztschr. f. physiol. Chem. 229: 25, 1934. (12) *Smyth, D. H.*: Biochem. J. 29: 2067, 1935. (13) *Hauptstein, P.*: Arch. f. Gynäk. 151: 262, 1932. (14) *Chang, H. C., and Wong, A.*: Chinese J. Physiol. 7: 151, 1933. (15) *Wong, A., and Chang, H. C.*: Chinese M. J. 47: 987, 1933. (16) *Wen, I. C., Chang, H. C., and Wong, A.*: Chinese J. Physiol. 10: 559, 1936. (17) *Chang, H. C.*: Proc. Soc. Exper. Biol. & Med. 32: 1001, 1935. (18) *Chang, H. C.*: Chinese J. Physiol. 13: 145, 1938. (19) *Hunt, R.*: Am. J. Physiol. 45: 197, 1917. (20) *Müller, F.*: Arch. f. d. ges. Physiol. 134: 289, 1910. (21) *Adler, L.*: Arch. f. exper. Path. u. Pharmacol. 83: 248, 1918. (22) *Berlin, E.*: Ztschr. f. Biol. 68: 371, 1918. (23) *Engelard, R., and Kutscher, F.*: Ibid. 57: 527, 1912. (24) *Alberts, G. G.*: Ergebn. d. inn. Med. u. Kinderh. 43: 114, 1932. (25) *Webster, M. D.*: J. Pharmacol. & Exper. Therap. 53: 340, 1935. (26) *Sherif, M. A. F.*: J. Physiol. 85: 298, 1935. (27) *Brdiczka, G.*: Arch. f. exper. Path. u. Pharmacol. 103: 188, 1924. (28) *Fontes, J.*: Compt. rend. Soc. de Biol. 102: 227, 1929; 103: 349, 1930. (29) *Kahlon, G.*: Arch. f. exper. Path. u. Pharmacol. 175: 189, 1934. (30) *Vasilin, C.*: J. de Physiol. et de Path. gén. 27: 80, 1929. (31) *Eagle, E.*: In press. (32) *Jeffcoate, T. N. A.*: J. Obst. & Gynaec. Brit. Emp. 39: 67, 1932. (33) *Frank, R. T., Bonham, C. D., and Gustavson, R. G.*: Am. J. Physiol. 74: 395, 1925. (34) *Reynolds, S. R. M.*: Endocrinology 16: 193, 1932. (35) *Reynolds, S. R. M.*: Am. J. Physiol. 100: 545, 1932. (36) *Zondek, B.*: Die Hormone des Ovariums und des Hypophysenvorderlappen, Vienna, 1930, J. Springer. (37) *Witherspoon, J. T.*: Proc. Soc. Exper. Biol. Med. 30: 1367, 1933. (38) *Gibbons, R. A.*: Lancet 1: 1160, 1934. (39) *Reynolds, S. R. M.*: Science 87: 537, 1938.

## THE CLOTTING MECHANISM OF MENSTRUAL FLUID\*

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THE fact that the menstrual discharge of normal women contains noneoagulated blood has aroused much study and speculation. The excellent reviews by Pickering,<sup>1</sup> Bartelmez,<sup>2</sup> and Dogliotti<sup>3</sup> indicate the numerous hypotheses that have been presented in explanation of this phenomenon. Four main factors have been variously regarded as being responsible for the presence of noneoagulated blood in menstrual blood. These may be summarized as follows:

1. The presence of an antieoagulant.<sup>4-6</sup>
2. A disturbance in the peripheral circulating blood.<sup>7</sup>
3. The presence of a lytic agent which dissolves the clot after it forms in the uterine cavity.<sup>5-11</sup>
4. The absence of one or more elements essential for the coagulation of normal blood.<sup>3, 12-17</sup>

As may be anticipated, agreement between the findings of the different investigators is wanting, and even among those supporting the same hypothesis there rarely is complete accord. Because of the many conflicting concepts and the recent development of more efficient methods for the study of blood coagulation, we believed it pertinent to reopen the problem.

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which did not contain menstrual blood. In three experiments, when the menstrual fluid was added to oxalated plasma together with calcium and thromboplastin, the clot that formed was found to have undergone lysis after incubation for sixteen to eighteen hours.

#### DISCUSSION

Almost all investigators accept the basic facts that normal blood plasma contains a substance, prothrombin, which is activated in the presence of calcium and thromboplastin to form an active coagulant, thrombin. Thrombin then reacts with fibrinogen to form the actual clot, fibrin. It is obvious that the absence of any one of these factors will result in noncoagulability of the blood. Likewise, the presence of any inhibitor (anticoagulant) will prevent the formation of a clot.

By means of some of the modern procedures employed in studies on blood coagulation, we have been unable to detect the presence of prothrombin, thrombin, fibrinogen, or anticoagulants in normal menstrual discharge. These findings apparently are in accord with the hypothesis advocated by various investigators that menstrual fluid is deficient in one or more factors essential for the coagulation of blood. Especially pertinent in this regard are the observations of Bell,<sup>16</sup> King,<sup>17</sup> and Dogliotti,<sup>3</sup> who, with crude and more indirect procedures, obtained data which are essentially similar to those discussed above.

The observation that practically all the factors essential for blood coagulation other than thromboplastin<sup>3</sup> and calcium<sup>22</sup> are absent in the menstrual fluid raises some interesting speculations. It can be assumed that these factors are missing because some mechanism exists which permits the endometrium to impair their passage from the circulating blood into the uterine cavity. However, the observations of Shaw<sup>10</sup> and others that clots can occasionally be found free in the uterine cavity suggests that an impermeability to prothrombin and other factors essential to blood coagulation need not necessarily exist.

Another mechanism which can account for the absence of blood coagulating factors in menstrual fluid would be one involving the utilization of these substances. That is, if the blood leaving the endometrium coagulated in a normal manner and subsequently underwent autolysis, prothrombin and all of the thrombin and fibrinogen would disappear from the menstrual discharge. The fact that clots can occasionally be found in the uterine cavity is in accord with such a point of view, as are the studies of numerous investigators who present evidence for the existence of lytic substances in menstrual fluid. The observation of an increased titer of tryptic enzymes in the circulating blood during the menstrual period<sup>7</sup> may be of some import in this connection. Likewise, in accord with this concept is our observation that a fibrin clot may occasionally undergo lysis when incubated with menstrual fluid. This hypothesis can account for all the observed facts relative to the fluidity and chemistry of the menstrual fluid. Thus, in cases where the bleeding from the endometrium is excessive, the rate of lysis may not be sufficiently rapid to disintegrate all the coagulated blood, and hence numerous clots may be expelled as has been frequently observed. This concept also may account for the conflicting observations of different

prepared thrombin solution. In no case did coagulation occur after incubation at 37.5° C. for sixteen to eighteen hours.

To eliminate the presence of a thrombin or fibrinogen inhibitor, 0.1 ml. of freshly prepared thrombin was added to a mixture of 0.1 ml. of fibrinogen solution and 0.1 ml. of menstrual fluid. Coagulation always occurred within twelve to fifty-five seconds (Table I). As a control, 0.1 ml. of freshly prepared thrombin was added to a mixture of 0.1 ml. of saline and 0.1 ml. of fibrinogen. In every case, the tubes containing menstrual fluid showed no delay in coagulation as compared with the saline controls. In fact, in many instances coagulation seemed slightly accelerated in the presence of menstrual fluid, which is in accord with the observations of others.<sup>3, 14, 16</sup> This experiment suggests that a thrombin inhibitor is not present in the menstrual fluid.

TABLE I. THE INFLUENCE OF MENSTRUAL FLUID ON COAGULATION

SUBJECT	TEST NUMBER	SALINE CONTROL* SECONDS	MENSTRUAL FLUID† SECONDS
A	1	24	21
	2	23	23
	3	21	19
B	4	18	18
	5	24	24
C	6	60	55
	7	13	14
D	8	17	16
	9	14	12
E	10	19	16
F	11	25	24
G	12	27	24
H	13	39	36
I	14	33	31

\*0.1 ml. saline + 0.1 ml. fibrinogen + 0.1 ml. thrombin.

†0.1 ml. menstrual fluid + 0.1 ml. fibrinogen + 0.1 ml. thrombin.

It may be noted from Table I that there is much variation in the coagulation times of the various tests. This may be due to the instability of the reagents, since the controls always give similar results.

To test for the presence of prothrombin, 0.1 ml. of fibrinogen solution was added to a mixture of 0.1 ml. of Quick's thromboplastic substance and 0.1 ml. of calcium and menstrual fluid, and allowed to incubate at 37.5° C. for sixteen to eighteen hours. However, coagulation did not occur in any instance. Since the possibility exists that the conversion of prothrombin may not occur because of an inhibitor of the reaction between prothrombin, thromboplastin, and calcium, 0.1 ml. and 0.2 ml. menstrual fluid was added to 0.1 ml. oxalated blood plasma, together with 0.1 ml. calcium and 0.1 ml. thromboplastin, and the mixture allowed to incubate. Clotting occurred in the five instances thus studied; the clotting time being the same as in the controls. This obviates the possibility that a prothrombin or thromboplastin inhibitor is present in menstrual fluid.

The fact that menstrual fluid is free of inhibitors of thrombin and thromboplastic activity makes it quite improbable that an anticoagulant is responsible for the presence of noneoagulated blood in the menstrual discharge.

In two experiments (Table I, Tests 7 and 11), it was noted that whereas coagulation of a mixture of fibrinogen and activated serum was not delayed by the menstrual fluid, after incubation for six to eight hours at 37.5° C., the tubes containing menstrual fluid showed a soft gelatinous, semifirmed clot, in contrast to the clots

FRIEDMAN TEST ON SPINAL FLUID IN CASES OF  
HYDATIDIFORM MOLE AND PREGNANCY  
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THE preoperative diagnosis of hydatidiform mole is often difficult. The use of qualitative and quantitative hormonal studies as an aid in diagnosis has been of some value, but there is need for a more exact method. It was, therefore, deemed advisable to investigate the Friedman test on the spinal fluid in cases of hydatidiform mole and to study its reaction in normal pregnancies, pregnancies complicated by cysts, fibroids, and purulent salpingitis, and in ectopic pregnancies. Owing to the fact that some of these conditions are rather rare and owing to the further difficulties in getting a large series of cases, this small group is presented as a preliminary report.

The recent literature on this subject is rather meager. Zondek and Mathieu mention the fact that normal pregnancy gives a negative spinal fluid Aschheim-Zondek reaction, while hydatidiform mole and chorioepithelioma yield a positive result. In 1929 Ehrhardt performed Aschheim-Zondek tests on the spinal fluid of 50 patients, including certain diseases of children as well as adults. This series contains 18 cases of pregnancy, essentially those complicated by general infections and toxemias. Four cases of toxemia of pregnancy and 1 case of pregnancy at three months complicated by carcinoma of the cervix gave positive A.P.R. I or A.P.R. III reaction (corpora hemorrhagica or lutea). In another article, Ehrhardt reports 2 cases of hydatid mole that gave positive Aschheim-Zondek reactions on the spinal fluid. However, we have not been able to find very many case reports with the use of the Friedman test in hydatid moles and pregnancy, and it is in this light that our observations are presented.

A routine spinal tap on every case of pregnancy in order to rule out suspected pathology is not advocated. However, it is felt that this procedure is of sufficient importance to the patient's welfare to warrant its performance on certain indications. In cases where the clinical picture or the quantitative hormonal studies are inconclusive, it is of special value. With this test a definite result can be obtained in forty-eight hours, or less. This saving of time may be of extreme importance in some cases. In cases where spinal anesthesia is to be performed for an operation, 5 to 10 c.c. of spinal fluid can be readily removed for examination without danger. This has been done in a number of our cases. In ambulatory patients, spinal puncture may be difficult, but can usually be managed. It has even been done in the patient's home, but this is not to be encouraged.

In this preliminary report, an attempt to demonstrate that the spinal fluid Friedman test is negative in pregnancies which are normal or complicated has been made. So far in our series it has been positive only in cases of hydatid mole. A positive spinal fluid Friedman test

investigators, since the presence or absence of various factors essential to blood coagulation would be dependent upon the rapidity of bleeding, the rate of disintegration of the blood clot, and the rate of destruction of the lytic agents.

#### SUMMARY

Menstrual fluid does not contain detectable amounts of fibrinogen, prothrombin, thrombin, or anticoagulants.

The significance of these findings is discussed, and it is suggested that the blood leaving the endometrium may clot, and that the clot subsequently undergoes digestion by some hypothetical lytic agent. When bleeding is excessive, the rate of lysis may be relatively slow, and undigested clots may be expelled.

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#### REFERENCES

- (1) *Pickering, J. W.*: Cyclopedia of Medicine, Philadelphia, 1933, F. A. Davis Co. 8: p. 761.
- (2) *Bartelmez, G. W.*: *Physiol. Rev.* 17: 28, 1937.
- (3) *Dogliotti, F.*: *Folia Gynaec.* 29: 119, 1932.
- (4) *Schickele, G.*: *Biochem. Ztschr.* 38: 169, 1912.
- (5) *Kross, I.*: *Surg., Gynec. & Obst.* 36: 217, 1923.
- (6) *Idem*: *Am. J. Obst. & Gynec.* 7: 310, 1924.
- (7) *Daniel, C., and Florian, S.*: *Rev. franç. de gynéc. et d'obst.* 30: 913, 1935.
- (8) *Whitehouse, H. B.*: *Lancet* 1: 877, 1914.
- (9) *Idem*: *Ibid.* 1: 1275, 1927.
- (10) *Shaw, W.*: *J. Physiol.* 60: 193, 1925.
- (11) *Rona, A., and Waldbauer, O.*: *Zentralbl. f. Gynäk.* 52: 997, 1928.
- (12) *Dienst, A.*: *München. med. Wchnschr.* 59: 2799, 1912.
- (13) *Kraul, L.*: *Zentralbl. f. Gynäk.* 49: 471, 1925.
- (14) *Cristea, A. M., and Denk, W.*: *Wien. Klin. Wchnschr.* 23: 234, 1910.
- (15) *Stickel, M., and Zondek, B.*: *Ztschr. f. Geburtsh. u. Gynäk.* 83: 1, 1920.
- (16) *Bell, W. B.*: *J. Path. & Bact.* 18: 462, 1913-14.
- (17) *King, J. L.*: *Am. J. Physiol.* 57: 444, 1921.
- (18) *Smith, H. P., Warner, E. D., and Brinkhaus, K. M.*: *J. Exper. Med.* 66: 801, 1937.
- (19) *Warner, E. D., Brinkhaus, K. M., and Smith, H. P.*: *Am. J. Physiol.* 125: 296, 1939.
- (20) *Ferguson, J. H., and Erickson, B. N.*: *Proc. Soc. Exper. Biol. & Med.* 40: 425, 1939.
- (21) *Quick, A. J.*: *Science* 92: 113, 1940.
- (22) *Bell, W. B.*: *Principles of Gynecology*, ed. 3, London, 1919, Baillière & Co.

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Quindlen, James P., and Taubenhaus, Leon: *Vincent's Cervicitis*, New Orleans M. & S. J. 92: 692, 1940.

These authors report a case of a 36-year-old colored female, a known syphilitic, with Vincent's cervicitis. The patient complained of abdominal pain for six days. Examination revealed a tender abdomen, slight bloody discharge, a cervix on whose surface craterlike irregularities could be felt. In the speculum the cervix appeared to be markedly ulcerated, the ulcers being covered with a moist, dirty, gray, foul-smelling membrane which would not peel off with ease. Smears and dark-field examinations were positive for Vincent's organisms. Smears and dark-field examinations made from the gums of the patient and her husband were both positive for Vincent's organisms. The cervix was treated with local applications of 2 per cent gentian violet and vaginal instillations of hydrogen peroxide. After thirty-six hours the inflammation was subsiding. After twelve days gentian violet was discontinued and 2 per cent arsphenamine in glycerin was used in its place. Twenty-one days after admission the cervix appeared normal and smears were negative. The patient was advised to discontinue the use of saliva as a lubricant for intercourse.

EUGENE S. AUER.

until April 25, when she began to bleed profusely. The uterus was only slightly enlarged and our impression was that we were dealing with a profuse menstrual bleeding. On May 6, 1940, the Friedman test on the urine as well as the Friedman test on the spinal fluid was negative. Because of these negative findings and the cessation of bleeding, the patient was discharged on May 6, 1940. She was readmitted on May 31, with a history of staining since her discharge from the hospital on May 6. The urine and spinal fluid Friedman tests were again negative (June 1). Nevertheless, she was curetted and remnants of placenta were found. No evidence of hydatid mole was present. She has been under observation for six months and has remained well.

CASE 4.—S. F., an 18-year-old female, para 0, gravida i, was admitted on March 23, 1939. Her last menstrual period was Dec. 10, 1938. She "spotted" on-and-off, from Jan. 10, 1940, to March 23, 1940. Physical examination revealed a uterus of four months' gravidity, soft and boggy, with a closed cervix. On March 30 a Friedman test on the urine was positive and a test on the spinal fluid was negative (10 c.c.). On June 30, 1939, the patient was seen in the follow-up clinic. The uterus was enlarged to the size of a seven months' gestation, and the fetal heart sounds were heard.

CASE 5.—R. M., aged 43 years, gravida iv, para iv, was admitted on April 1, 1940, for a therapeutic abortion. Her last menstrual period was on Jan. 8, 1940. The uterus was the size of a three months' gestation. On March 8 the Friedman test on the urine was positive. On April 3, the Friedman test on the spinal fluid (5 c.c.) was negative. On April 3 a fundectomy was performed. A fetus 7 cm. long was found.

CASE 6.—E. K., 29-year-old female, para i, gravida ii, was admitted to the hospital on March 27, 1940. Her last menstrual period was on Feb. 25, 1940. She complained of severe pain in the lower abdomen. There was no history of bleeding. The uterus was only slightly enlarged. She was only four days past her expected period. On April 1, 1940, a Friedman test on the urine was positive. On April 1, 1940, the Friedman test on the spinal fluid was negative. After one week's rest in bed, the patient was discharged. She was seen in the follow-up clinic in July, 1940, and the uterus was the size of a four months' gestation. In September, 1940, the uterus was the size of a six months' gestation. The fetal heart sounds were heard.

CASE 7.—A. M., a 32-year-old female, gravida ii, para i, was admitted to the hospital on April 16, 1940. Her last menstrual period was on Dec. 25, 1939. She "spotted" on Feb. 1, 1940, and continued to do so for one week. She was well again until four weeks prior to admission, at which time, the "spotting" returned and continued until the time of admission. On admission, the uterus reached the umbilicus. This was larger than the period of amenorrhea would indicate. Hydatid mole was suspected. On April 19, 1940, the Friedman test on the urine was weakly positive. On April 19, 1940, the Friedman test on the spinal fluid (5 c.c.) was negative. On April 19, 1940, a normal fetus and placenta were delivered spontaneously (four months' size fetus).

CASE 8.—M. L., a 37-year-old female, gravida iii, para ii, was admitted to the hospital on April 22, 1940. Her last menstrual period was on March 8, 1940. Her chief complaint was pain in the lower abdomen. No bleeding was present. She was sixteen days past her expected period. The uterus was irregularly enlarged to the size of a twelve weeks' gestation. The right kidney was ptosed. On April 25, 1940, the Friedman test on the urine was positive. On April 26, 1940, the Friedman test on the spinal fluid was negative. On April 26, 1940, a supravaginal hysterectomy was performed. The pathologic report was "myomatous uterus with early pregnancy."

CASE 9.—H. T., a 23-year-old female, gravida i, was admitted on May 6, 1940. Her last menstrual period was on Jan. 23, 1940. The patient had skipped her February and March periods, but on April 5, she began to bleed continuously

was also obtained in a case of seminoma occurring in a male with an ectopic testicle (proved by operation and autopsy). Our series of cases is rather small, but we hope to add to this group in the near future.

The technique used in performing this test is quite simple. Five to 10 c.c. of spinal fluid, preferably 10 c.c., was injected into the vein of the ear of a virgin rabbit, weighing about 1,600 Gm. No preparation of the cerebrospinal fluid was carried out. In forty-eight hours, the animal was sacrificed (intravenous injection of air was utilized for this purpose). The ovaries were then examined for A.P.R. II and III reactions. Unusually large A.P.R. I reactions were interpreted as negative, but repetition of test was found advisable in these cases. In our series this test was found to be negative in all the cases of normal pregnancy, pregnancy complicated by cysts, tumors, infections, and ectopic pregnancy. It was positive in cases of hydatid mole. The exact mechanism to explain these phenomena is unknown. The reason why the spinal fluid in cases of hydatid mole and chorioepithelioma contains sufficient anterior pituitarylike hormone to give a positive test, and other forms of pregnancy do not, is at present under investigation by us. We do know, however, as is exemplified in Case S. M. that in hydatid mole the Friedman test in the urine may be weakly positive and the prolan A and B titers moderately low and still the spinal fluid Friedman test strongly positive. Subsequent findings corroborated the specificity of the spinal fluid Friedman test in this case, and it was upon the basis of the latter that proper treatment was instituted early.

In this work, it was important to confirm the fact that normal pregnancy, ectopic pregnancy, and pregnancies complicated by cysts, tumors, or inflammation gave negative spinal fluid Friedman tests and that both early and advanced pregnancies also gave negative results. Urinary Friedman tests, findings at operations or subsequent parturition were used as checks upon these observations. To illustrate these facts, the following brief case histories are presented:

CASE 1.—S. M., aged 48 years, gravida ii, para i, was admitted to Beth Israel Hospital on Dec. 7, 1939. Her last menstrual period was Aug. 10, 1939. She "spotted" on September 10 and 11 and also on October 5 and November 15. From November 15 to December 7 (time of admission), there was continuous slight bleeding. Physical examination on admission was negative except for the uterus which seemed slightly larger than should be expected for the period of amenorrhea. The fetal heart sounds were not heard, nor were the fetal parts felt. Friedman test on the urine, done December 8, was reported weakly positive. The spinal fluid Friedman test, done on December 9, was strongly positive. Quantitative A.P.R. III was reported as 8,000 M.U. per liter. On December 12, because of the positive spinal fluid Friedman test, despite weakly positive urinary Friedman test and only 8,000 M.U. A.P.R. III in the twenty-four-hour urine specimen, the uterine cavity was explored digitally and a hydatid mole was expressed.

CASE 2.—R. M., aged 30 years, para ii, gravida iv, was admitted to Beth Israel Hospital January 10, with chief complaint of vaginal bleeding of one week's duration. Her last menstrual period was Oct. 1, 1940. The uterus was about the size of a six to eight weeks' gestation, and she had tenderness in the right lower quadrant. A urinary Friedman test, performed on January 9, was strongly positive. The uterus was curetted on January 11, and the pathologist reported the presence of hydatid mole. Spinal fluid Friedman test done on the fourth postoperative day was positive. Spinal fluid and urine Friedman tests done eight weeks later, on March 7, were negative. At the time of writing, the patient is well and has not been bleeding.

CASE 3.—I. J., a 25-year-old female, gravida ii, para i, was admitted to Beth Israel Hospital on May 2, 1940. On March 31, 1940, a dilatation and curettage was done for uterine bleeding, and hydatid mole was found. The patient was well

# INOCULATIONS OF INTESTINAL AND VAGINAL TRICHOMONADS INTO THE HUMAN VAGINA

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THE opinion is widespread, particularly among clinicians, that the vaginal and intestinal trichomonads are identical organisms, their apparent differences resulting from conditioning factors of their respective environments. This opinion has considerably influenced the treatment of vaginal trichomoniasis with regard to prophylaxis and the prevention of reinfection. On the other hand, certain laboratory and clinical evidence has been presented which indicates that *Trichomonas vaginalis* and the intestinal trichomonad, *Trichomonas hominis*, are distinct species. The establishment of the validity of either theory is essential to the proper understanding and management of the clinical condition, trichomonas vaginitis.

The studies herein reported are an attempt to approach this problem directly, by the inoculation under similar conditions, of both the vaginal and intestinal trichomonads into the vaginas of human subjects.

Three groups of experiments were conducted.

1. *Trichomonas hominis* was implanted into trichomonas-free vaginas.
2. *Trichomonas hominis* was implanted into vaginas harboring *Trichomonas vaginalis*.
3. *Trichomonas vaginalis* was implanted into trichomonas-free vaginas.

## MATERIAL AND METHODS

The subjects for these experiments were volunteers, previously discharged from the postnatal clinic of the Department of Obstetrics of Jefferson Medical College Hospital.

A total of 50 patients was selected for these experiments, forty of whom were within the three-month postnatal period. Twenty-five were trichomonas-free, while 25 harbored *T. vaginalis*.

These patients were first thoroughly studied with regard to abnormalities of the lower genital tract. They were instructed not to douche and to stop all other local treatment. After several days they were questioned concerning local symptoms. At this time, the lower genital tract was exposed with a speculum and examined with particular reference to the condition of the vaginal mucosa and the cervix, as well as the amount and character of the discharge. Gram-stained smears were prepared from the vaginal secretion, and the bacterial flora subsequently graded according to Schröder's classification.<sup>1</sup> The pH of the vagina and external cervical os were determined by the glass electrode method. In the vagina, three sites were chosen: the midvagina, the anterior fornix, and the posterior fornix. The vaginal material was then examined for the presence of trichomonas, by the use of the fresh wet smear and by culture. This procedure was repeated on each visit preceding the inoculations and on every subsequent visit throughout the period of observation.

until the date of her admission on May 6, 1940. The uterus was enlarged and a cystic mass was felt in the right adnexal region. A diagnosis of ovarian cyst complicating pregnancy was made. May 9 both urinary and spinal-fluid Friedman tests were negative. At operation, a right ovarian cyst and purulent salpingitis were found. There was no evidence of pregnancy.

CASE 10.—F. D., a 35-year-old female, gravida i, para i, was admitted to the hospital on Sept. 23, 1940. Her history was typical of an ectopic gestation and this diagnosis was made preoperatively. On September 26, the Friedman test on the urine was positive. On September 27, the Friedman test on the spinal fluid was negative. The patient was operated upon on September 28 and an ectopic pregnancy (eight weeks) was found in the left Fallopian tube.

#### DISCUSSION

Two cases of hydatid mole with positive Friedman tests on the spinal fluid were described. Another case of hydatid mole that had been curetted and practically cured except for a small piece of retained placenta was reported. In this case, the Friedman test on the spinal fluid was negative; subsequent findings and follow-up corroborated the absence of hydatid mole. Case 10 demonstrated that the spinal fluid Friedman test is negative in ectopic gestation. Pregnancy cases in which amenorrhea ranged from four days to six months were presented. The course of events in these cases showed no evidence of hydatid mole or chorioepithelioma, and all gave negative spinal fluid Friedman reactions but positive urinary Friedman tests. In a case of suspected pregnancy (amenorrhea of two months), both urine and spinal fluid Friedman tests were negative. This patient had an ovarian cyst and "pus tubes." Neither of these two conditions had any influence on the spinal fluid Friedman test. Case 8 turned out to be a myomatous uterus with pregnancy; the spinal fluid Friedman reaction was negative, indicative of the fact that fibroids do not influence this reaction.

#### SUMMARY

1. The Friedman test on the spinal fluid was positive in two cases of hydatid mole and negative in a cured case of hydatid mole.
2. This test was negative in one case of ectopic pregnancy.
3. Normal pregnancy, both early and late, yielded a negative spinal fluid Friedman test.
4. The spinal fluid Friedman test was uninfluenced by myomas or ovarian cysts complicating pregnancy.
5. Cases of ovarian cyst or "pus tubes" with amenorrhea and without pregnancy gave negative spinal fluid Friedman test.
6. One case of seminoma in a male gave a positive spinal fluid Friedman test.
7. The findings in this small series of cases are presented as a preliminary report.

#### REFERENCES

- (1) Zondek, B.: "Hormone des Ovariums und des Hypophysenvorderlappens," ed. 2, Vienna, 1935, J. Springer, pp. 360 and 554. (2) Mathieu, A.: AM. J. OBST. & GYN. 37: 654, 1939. (3) Zondek, B.: J. A. M. A. 108: 607, 1937. (4) Ehrhardt: Med. Klin. 27: 426, 1931. (5) Ehrhardt: Klin. Wchnschr. 8: 2330, 1928.



*Group 2.—*

In this group an attempt was made to transfer *T. hominis* to an environment suitable to the growth of trichomonas, as indicated by the presence of *T. vaginalis* in the vagina. Twenty-five trichomonas-positive patients were used.

*Clinical Status Before Inoculation.*—Three patients were symptom-free, despite the presence of *T. vaginalis*. Ten noticed a slight discharge, 8 a moderate amount, and 4 complained of a profuse discharge. In the last group, 3 also suffered from pruritus.

The discharge was thick and white in 1 instance, thin and mucopurulent in 17, slight in 5, and of moderate quantity in 12. Seven patients had the characteristic profuse, bubbly, mucopurulent, or grayish discharge.

Irritation of the vaginal mucosa was observed in 14 of these patients, 2 of whom showed "flea-bitten" areas. In 3, the vagina was only slightly inflamed, and in 8 it appeared grossly normal. The cervix was eroded in 21 patients, the degree being classified as slight in 4, and moderate in 17.

In Table II is given the range of vaginal and cervical pH readings, correlated with the type of bacterial flora.

TABLE II. *T. VAGINALIS*-POSITIVE PATIENTS

BACTERIAL FLORA		pH		NO. OF INOCULATIONS	RESULTS	DAYS OBSERVED AFTER INOCULATION
GRADE	NO.	VAGINAL	EXTERNAL CERVICAL OS	48-72-HOUR CULTURE	CULTURE	
I	0	—	—	—	—	—
II	2	4.9-5.9	6.8-7.0	3	Neg.	12- 26 (2 Patients)
III	20*	5.3-6.1	6.0-8.0	3	Neg.	7- 16 (6 Patients)
						26- 54 (7 Patients)
						77-80 (2 Patients)
						247-281 (2 Patients)
Not known	3	5.2-6.0	7.5-7.9	3	Neg.	19- 28 (2 Patients)
						77 (1 Patient)

\*Three patients failed to return for check-up.

*Clinical Status Following Inoculation.*—Culture studies made throughout the period of observation subsequent to the inoculations revealed that all patients remained free of *T. hominis*, though continuing to harbor *T. vaginalis* in large numbers. In this group no significant change in symptoms or signs occurred following inoculation.

The 4 strains of *T. hominis* employed in the experiments of Groups 1 and 2 were established experimentally in the intestine of kittens.<sup>2</sup>

*Group 3.—*

It was also desired to determine whether or not *T. vaginalis* could be successfully implanted in vaginas refusing to tolerate *T. hominis*. Consequently, 10 trichomonas-free patients in whom *T. hominis* inoculations were unsuccessful, were submitted to one direct *T. vaginalis* inoculation from freshly collected discharge. Three separate donors were used in these experiments.

Secretion was collected on a swab from the positive patient and mixed thoroughly with 2 to 3 c.c. of physiologic saline solution. Approximately 1 c.c. of this material was used to swab the posterior portion of the vagina of the negative patient.

*Clinical Status Following Inoculation.*—The various clinical and laboratory findings in these patients previous to, and following, the inoculations are given in Table III.

*Trichomonas vaginalis* infestation was produced in 8 patients, who remained positive for the flagellates over varying periods of time (Table III). Three of the inoculated subjects showed trichomonas at seven days, and 4 showed them within three weeks. The eighth, who may have acquired her flagellates elsewhere, remained negative until the thirty-fifth week. Two other recipients remained consistently negative over periods of four and nine weeks, respectively.

Trichomonads were then inoculated into the vagina, by the introduction of approximately 1 c.c. of material from the richest part of a forty-eight- to seventy-two-hour culture of *Trichomonas hominis*.<sup>2</sup> Four strains were used. Ten individuals of the trichomonas-free group, in whom *T. hominis* had failed to survive, were also directly inoculated with approximately 1 c.c. of discharge from a trichomonas-positive donor.

Other data, including experiments relating to the viability of the trichomonads used for the inoculations, have been reported elsewhere.<sup>2</sup>

## RESULTS

### Group 1.—

In the experiments in this group an attempt was made to establish an infestation of *Trichomonas hominis* in 25 *T. vaginalis*-free patients.

*Clinical Status Before Inoculation.*—A fairly diverse series of patients was represented in this group. Five were entirely symptom free, 16 noticed a slight discharge, and 3 complained of a moderate amount of leucorrhea. One patient, having a rather profuse flow, was found infected with monilia.

On examination, the following findings were noted: The discharge was entirely normal in 7 patients. In 10, the discharge was slight in amount, thin in consistency, and mucopurulent in character. In 7 others, with a mucopurulent discharge, it was moderate in amount in 4, and profuse in 3. The characteristic cheesy type of discharge was noted in the patient with monilia.

The vaginal mucosa was normal in 20 patients, slightly reddened in 3, and showed a marked irritation in 2. The cervix was normal in 10 patients, in 7 there was a slight erosion, and in 8 the erosion was of a moderate degree.

The pH determinations of the vagina and external cervical os are given in Table I, along with the types of bacterial flora.

*Clinical Status Following Inoculation.*—Repeated inoculations of *Trichomonas hominis* resulted in the production of some symptoms and signs of vaginal irritation in a number of patients, despite the fact that all remained negative for trichomonas throughout. The distribution of the various signs and symptoms were as follows: Five remained entirely free of symptoms, and 5 noticed an increase in discharge, which was quite marked in 1 patient. In 4, a profuse, thin, mucopurulent discharge occurred. Slight vaginal inflammation resulted in 6 instances, while in 8 patients the inflammatory reaction was more marked. Little or no change occurred in regard

TABLE I. T. VAGINALIS-FREE PATIENTS

BACTERIAL FLORA		pH		NO. OF INOCULATIONS	RESULTS		DAYS OBSERVED AFTER INOCULATION
GRADE	NO.	VAGINAL	EXTERNAL CERVICAL OS	48-72-HOUR CULTURE	SMEAR	CULTURE	
I	2	4.4-5.0	6.5-6.8	2-3	Neg.	Neg.	35-70 (2 Patients)
II	4	4.1-5.3	6.4-7.2	3	Neg.	Neg.	12-35 (2 Patients)
III	14*	5.2-6.4	6.0-8.0	3	Neg.	Neg.	94-203 (2 Patients)
							18-26 (3 Patients)
							30-44 (4 Patients)
							70-133 (3 Patients)
Not known	5	4.4-6.1	6.8-7.5	3	Neg.	Neg.	59 (1 Patient)
							112-124 (2 Patients)
							297-313 (2 Patients)

\*Four patients failed to return for check-up.

to the cervix, nor did any significant shift in pH occur. The occurrence of signs and symptoms of vaginal inflammation was attributed to the metabolic products of the bacteria and flagellates present in the cultures.

Subsequent to direct inoculation, symptoms and signs became aggravated in 2 patients (Cases 3 and 6). In 3 (Cases 1, 6, and 9), the discharge became mucopurulent, being also bubbly in character in Patients 1, 5, and 6. In Cases 6, small hemorrhagic spots, so-called "flea-bitten" areas, appeared on the vaginal cervix. Monilia was inadvertently transferred to two patients (Cases 2 and 8); an acute exacerbation of symptoms followed.

#### SUMMARY

1. Twenty-one *T. vaginalis*-free patients remained negative after repeated intravaginal inoculations from cultures of *T. hominis*.
2. Twenty-two patients positive for *T. vaginalis* remained likewise negative for *T. hominis* after similar inoculations.
3. *T. vaginalis* was easily transferred to a series of negative women by direct inoculations of positive vaginal secretion.
4. It is concluded that contamination from the rectum is not a method of acquiring vaginal trichomoniasis.
5. These experiments also support the opinion that *T. vaginalis* and *T. hominis* are separate and distinct species.

#### CONCLUSIONS

The evidence which has been presented in these experiments indicates that the intestinal trichomonad, *T. hominis*, is unable to establish itself in the human vagina, even under conditions which are favorable to *T. vaginalis*.

Such results are of considerable clinical significance in that they indicate that contamination from the rectum is not a means by which vaginal trichomoniasis is acquired, as previously claimed.<sup>3</sup> The results also constitute further evidence of specific difference between *T. hominis* and *T. vaginalis*.

The facile implantation of *T. vaginalis* from one patient to another, as shown here, is important, especially in view of the reported difficulty of producing similar infestations from pure cultures of the organism.<sup>4</sup>

The characteristic symptoms and signs, frequently described as those of a trichomonas vaginitis, developed in only two patients after direct transmission. Others have reported a higher incidence in the occurrence of these characteristic manifestations.<sup>5</sup>

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#### REFERENCES

- (1) Schröder, R., Hinricks, B., and Kessler, R.: Arch. f. Gynäk. 94: 126, 1926.
- (2) Stabler, R. M., Feo, L. G., and Rakoff, A. E.: Am. J. Hyg. Accepted for publication.
- (3) Karnaky, Karl John: Urol. & Cutan. Rev. 38: 174, 1934.
- (4) Trussell, R. E., and Plass, E. D.: AM. J. OBST. & GYNEC. 40: 883, 1940.
- (5) Kessel, J. F., and Gafford, J. A.: Ibid. 39: 1005, 1940.

TABLE III. PATIENTS INOCULATED WITH T. VAGINALIS FOLLOWING UNSUCCESSFUL T. HOMINIS IMPLANTATIONS

PATIENT	SYMPTOMS			SIGNS				PH		BACT. FLORA	NO. DAYS OBSERVED BEFORE INOC.	DAY PATIENT OBSERVED POSITIVE	NO. DAYS PATIENT POSITIVE
	DIS-CHARGE	PRURITUS	BURN-ING	AM <sup>3</sup> T DISCH.	TYPE	VAG. INFL.	CERVICAL EROSION	VAG.	CERV. OS				
1. Before	+	-	-	+	thin white	-	+	5.6-6.1	7.5	III	21	7	40
2. Before	-	-	-	+	m.pur.* bubbly	-	+	5.0-5.3	7.1	III			
After	+++	-	-	+++	thick white thin m.pur.	+	+++	4.4-4.7	7.2	II	26	7	82
3. Before	-	-	-	++	m.pur. bubbly	-	-	4.1-4.4	7.3	II			
After	+	+	+	+++	m.pur. bubbly	-	-	4.9-5.4	5.9	Monilia	16	7	82
4. Before	+	++	-	+++	m.pur. bubbly	++	++	(Dis.) 6.2-6.4	6.6	III	21	19	19
After	++	+++	-	+++	m.pur. cheesy	+++	+++	4.4-5.6	5.0	III		Menstruating	
5. Before	+	-	-	++	m.pur. cheesy	+++	+++	4.4-5.5	(Dis.) 6.4	Monilia	21	7	91
After	+	-	-	++	thin white	-	-			III			
6. Before	+++	-	-	+++	white bubbly	+	+	4.1-4.6	6.4	Monilia			
After	+++	-	-	+++	white mucoid thin m.pur. bubbly	+	+	5.2-6.0	6.9	II	167		
7. Before	+	-	-	+	thin m.pur. bubbly	-	+	4.4-5.0	6.5	II	43	28	28
After	+	-	-	+	thin white	+	+	5.2-5.5	7.2	I		Negative	
8. Before	-	-	-	+	thin white	+	+			II	21	19	28
After	+	+	-	++	thick white m.pur. cheesy	+	+	4.2-4.7	6.5	II			
9. Before	+	-	-	++	thin white	+	+	4.4-5.5	7.6	II	21	16	16
After	+	-	-	++	m.pur. cheesy	++	-	4.3-5.1	7.5	III	118	21	49
10. Before	+	-	-	+	white mucoid thin m.pur.	+	+	4.4-4.8	7.4	III			
After	+	-	-	+	thin m.pur.	+	+			Monilia	128	250	250
*m.pur., mucopurulent.	+	-	-	+	thin m.pur.	-	+	4.6-4.9	6.9		12	Negative	61
					thin m.pur.	-	+	4.7-5.4	7.0				61
					thin m.pur.	-	+	4.6-5.3	6.5	III			
					thin m.pur.	-	+	5.1-5.4	7.5	III			

TABLE I. THE CONTRACTILE RESPONSE OF THE PREGNANT UTERUS TO POSTERIOR PITUITARY EXTRACT IN RELATION TO THE DURATION OF LABOR

RESPONSE	NO.	MEAN DURATION OF LABOR HR.	MINIMS OF EXTRACT							
			1		1.5		2		3	
			PATIENTS NO.	MEAN DURATION OF LABOR HR.	PATIENTS NO.	MEAN DURATION OF LABOR HR.	PATIENTS NO.	MEAN DURATION OF LABOR HR.	PATIENTS NO.	MEAN DURATION OF LABOR HR.
No	7	21.3 ± 9.6	2	24.5	1	10.0	2	29.2	2	15.6
Yes	19	9.3 ± 5.4	4	11.9	4	6.8	5	10.0	6	8.5
Clonic	11	6.9 ± 4.8	1	1.8	3	4.8	4	13.0	3	7.2
Tetanic	8	12.5 ± 4.6	3	15.3	1	13.0	1	11.0	3	9.9
Incomplete	7	11.2 ± 3.3	2	12.3	1	13.0	1	11.0	3	9.9
Complete	1	21.5 ± 0.0	1	21.5	0	—	0	—	0	—

Recording the influence of the character of the contractile response of the uterus to posterior pituitary extract, nineteen days before labor, upon the duration of labor. Observations upon 26 primigravidas, arranged according to the amount of extract employed. Note: (a) Shortness of labor of patients experiencing a response, compared with length of labor of those who had none; (b) shortness of labor of women exhibiting a clonic reaction, compared with ones having a tetanic response.

# THE CONTRACTILE RESPONSE OF THE UTERUS TO POSTERIOR PITUITARY EXTRACT DURING LATE PREGNANCY AND ITS RELATION TO THE DURATION OF LABOR

A STUDY OF 26 PRIMIGRAVIDAS WITH THE LÓRÁND TOCOGRAPH

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WHILE studying the activity of the uterus which takes place during late pregnancy, posterior pituitary extract was administered to a series of patients in order to determine the character of the contractile response which the uterus might exhibit at that time.

Some individuals responded and others did not. It was possible to classify the positive responses in several categories, depending upon whether the reaction was purely clonic, or had a tendency toward tetany; and if the latter condition occurred, whether or not the spasm interfered with the registering of the clonic contractions.

This variation in response to the drug, and the well-known variation in uterine activity observed at the time of labor, suggested that there might be a correlation between the two. Would the patient whose uterus failed to respond to posterior pituitary extract before labor be less sensitive to the stimulus of labor than one whose uterus did react? And would there be a significant relation between the character of any positive responses during pregnancy, and the kind of contractions observed during labor? The present study attempts to throw light upon these questions.

## MATERIALS AND METHODS

The records of uterine activity were made between June 30, 1939, and July 9, 1940, upon 26 women, pregnant for the first time, and residing in the Sheltering Arms Home, Philadelphia. The observations were recorded with the latest model Lóránd tocograph.<sup>1</sup>

Each patient rested upon her bed for ten minutes before the recording was begun. After a fifteen-minute control period of recording, and without removing the tocograph, she received an intramuscular injection of posterior pituitary extract (obstetric pituitrin, Parke Davis & Co.) in the upper arm. The tocographic record was continued for a period of thirty minutes following the injection. The pituitrin was assayed at 10 international units per cubic centimeter of solution.

The majority of the patients were delivered in the Hospital of the University of Pennsylvania. The study was limited to primigravidas who exhibited no evidence of cephalopelvic disproportion; ones who were delivered vaginally and whose infants at birth weighed between 2,500 and 4,000 Gm. The average age of the women was  $20 \pm 4.2$  years. Their uterine activity was recorded on an average of  $19 \pm 5.7$  days before labor. Each individual supplied only a single record for the present analysis.

vary with the duration of pregnancy. Of 63 treatments administered at weekly intervals to the present 26 patients, and to 6 additional ones, prior to the thirty-second week of gestation, the dose in no instance exceeding 3 minims, only 6 (9.5 per cent) were followed by any sensation of abdominal constriction and none by any pain. On the other hand, of 223 treatments given to the same patients after the thirty-first week of gestation, 51 (22.8 per cent) resulted in a feeling of tightness and 11 others were followed by a definite sensation of pain. The pain in all instances was mild except in the case of one patient whose uterus was extremely tense throughout pregnancy. Her pain was so severe after the first two tracings that later treatments had to be abandoned.

Another patient, not included in the above group, whose uterus was not tense, experienced a severe and prolonged uterine spasm, on the fourteenth day before labor, following a dose of only 1.5 minims of pitocin (Parke, Davis & Co.).

These observations suggest that the test dose of posterior pituitary extract should be small if painful responses are to be avoided. However, even where we have employed a dose as large as 3 minims no untoward reaction other than pain was noted.

In previous reports it was shown that the pregnant uterus becomes unusually active<sup>3</sup> and reactive<sup>2</sup> to posterior pituitary extract during the week or two immediately prior to the onset of clinical labor. The nineteenth day before labor, therefore, was selected as the time to study the present patients, in order to avoid the later period. A period earlier than the nineteenth day might have served equally well.

In view of the small number of observations, and because the study is limited to primigravidas, it cannot be said that the present inferences necessarily can be applied generally. Nevertheless, the observations do not appear to be illogical, nor do they seem to be out of line with others that we have made thus far. The results are presented for what they may be worth. Undoubtedly it will be necessary to assemble additional data, and rule out the influence of the many variables which influence response, before the relationship between response and the character of the contractions which occur during labor is fully understood, and before the method should be employed clinically for predicting the nature of the impending labor.

#### SUMMARY AND CONCLUSIONS

1. The uterine activity of a consecutive series of 26 primigravidas was registered with a Lóránd tocograph, approximately nineteen days before the onset of labor, while the patients were receiving intramuscular injections of posterior pituitary extract.

2. The incidence of responses and the character of the positive ones were correlated with the duration of labor.

3. Individuals experiencing a response had significantly shorter labors than those who gave no response.

4. Women having an uncomplicated clonic reaction had significantly shorter labors than those whose responses exhibited a tendency toward tetanic spasm.

## RESULTS

The incidence of responses and the character of the positive ones are summarized in Table I, and arranged according to dosage, where they are correlated with the duration of labor.

Positive responses are classified as: (a) Clonic, (b) incomplete tetanic, and (c) complete tetanic.<sup>2</sup>

A *clonic* response is characterized by a series of rhythmically recurring contractions, not associated with any increase in the tension of the uterus.

An *incomplete* tetanic response is characterized by clonic contractions associated with an increase in the tension of the uterus, which is indicated by an elevation of the valleys between the waves. The increase in tension in this instance, however, does not prevent the registration of any of the clonic contractions.

A *complete* tetanic contraction is characterized by the presence of clonic contractions, associated with an increase in tension which blocks out one or more of the clonic contractions.

Correlation of the mean duration of labor of all patients irrespective of the amount of posterior pituitary extract which they received, with the character of their responses, Columns 1 and 2, Table I, indicates that the women, experiencing no response had significantly longer labors than those who gave a response. The difference in the length of the labors in the two groups was twelve hours, with a standard error of 3.9 hours.

The patients experiencing any tetanic tendency whatever had labors of a mean duration of 12.5 hours, whereas those having an uncomplicated clonic reaction, had a mean duration of only 6.9 hours. The difference is 5.6 hours, with a standard error of 2.2 hours. Since this difference is nearly three times its standard error, for practical purposes, it might be considered statistically significant.

It is of interest, if not statistically significant, that the mean duration of labor of the 7 patients experiencing an incomplete tetanic response, was shorter than that of the one patient having a complete tetanic reaction.

## DISCUSSION

The present series of observations, admittedly, is small, but this disadvantage is offset, to a certain extent at least, by the uniformity of the material.

In a previous communication,<sup>2</sup> we have indicated the roles played by individual variability, parity, the duration of pregnancy, the presence of labor and other factors, which influence the contractile response of the pregnant uterus to oxytocic drugs.

The present patients were all primigravidas; they were close to the same age, and lived under uniform conditions during the period covered by the study. Another advantage in utilizing this group lies in the fact that the majority of the patients were delivered under our own supervision, which made it possible to secure uniform and satisfactory records of the character and duration of their labors.

The question may be raised as to the suitability of the duration of labor as a measure of the efficiency of the uterine contractions at that time. The answer is that we were unable to find any other more practical measuring rod.

The doses of posterior pituitary extract employed in the present study varied from 1 to 3 minims. These amounts produced a sensation of abdominal constriction in 9 instances, and a feeling of pain in one case. No other untoward effects were noted.

Both the incidence and degree of subjective sensation, resulting from the administration of posterior pituitary extract during pregnancy,



TABLE I. DISTRIBUTION OF CASES

Distribution	130 VAGINAL HYSTEREC- TOMY		348 SUPRAVAGINAL HYSTEREC- TOMY		1,436 PANHYSTER- ECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Resident Staff	81	4.23	119	6.2	905	47.2	1,105	57.7
Visiting Staff	49	2.56	229	11.9	531	27.7	809	42.3
Combined Staffs	130	6.79	348	18.2	1,436	74.9	1,914	100.0
Color Distribution								
White	122	93.8	246	70.6	987	68.8	1,355	70.8
Colored	8	6.2	102	29.4	449	31.2	559	29.2
Parity								
Para 0	6	4.6	159	45.6	368	25.6	533	27.8
Para i plus	124	95.4	189	54.4	1,068	74.4	1,381	72.2

marked. It should be noted also that vaginal hysterectomy cases are spread out over the fifth, sixth, and seventh decades of life when the pelvic supports participate in the general tendency of pelvic tissues to thin out and relax. The two total hysterectomies on young girls were done for intractable bleeding in one instance and in the other for pelvic structures hopelessly damaged by pelvic infection.

The incidence of diagnosis shown in Table III illustrates the relative frequency of occurrence of common gynecologic conditions. Chronic cervicitis is purposely omitted, because in the pathologic reports the diagnosis was made in practically every case in which the cervix was

TABLE II. AGE DECADE DISTRIBUTION

	130 VAGINAL HYSTEREC- TOMY		348 SUPRAVAGINAL HYSTEREC- TOMY		1,436 PANHYSTER- ECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Second decade 10-19					2	0.1	2	0.1
Third decade 20-29	4	3.1	31	8.0	161	11.2	196	10.2
Fourth decade 30-39	31	23.8	145	41.6	638	44.5	814	42.5
Fifth decade 40-49	40	30.7	140	40.2	512	35.7	692	36.1
Sixth decade 50-59	23	17.7	31	8.9	108	7.53	162	8.4
Seventh decade 60-69	28	21.5	1	0.3	15	1.04	44	2.29
Eighth decade 70-79	4	3.07					4	0.20

TABLE III. INCIDENCE OF DIAGNOSIS

	130 VAGINAL HYSTEREC- TOMY		348 SUPRAVAGINAL HYSTEREC- TOMY		1,436 PANHYSTER- ECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Relaxed vaginal outlet	127	97.8	103	29.6	890	62.0	1,120	58.5
Myoma	33	25.4	242	69.5	788	54.9	1,063	55.6
Salpingitis			127	36.5	356	24.8	483	23.8
Endometriosis	8	6.15	41	11.8	104	7.3	153	7.9
Ovarian tumors			18	5.2	50	3.5	68	3.6
Carcinoma of fundus			5	1.4	21	1.5	26	1.4
Carcinoma of cervix					7	0.49	7	0.36
Prolapse	118	90.8	1	0.3	93	6.5	212	11.0

5. Seven patients having a mild degree of tetanic reaction had, on the average, shorter labors than one individual who showed a more severe degree of tetanus.

6. From these observations it might be concluded that, under the conditions of this study, there existed a significant relation between the character of the uterine contractile response to posterior pituitary extract administered during late pregnancy and the character of labor as indicated by its length.

The author is indebted to Dr. Dorothy L. Ashton for the privilege of studying the patients on her service at the Sheltering Arms Home.

#### REFERENCES

- (1) Lóránd, S.: *Monatschr. f. Geburtsh. u. Gynäk.* 103: 137, 1936. (2) Murphy, D. P.: *AM. J. OBST. & GYNEC.* 41: 274, 1941. (3) *Idem*: *Surg., Gynec. & Obst.* 70: 129, 1940.

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## A STATISTICAL REPORT OF 1,914 CASES OF HYSTERECTOMY

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ON TWO previous occasions, statistics on hysterectomy have been reported from this department which included all cases up to 1935.<sup>1, 2</sup> This report covers the last five-year period ending Jan. 1, 1940, and comprises 1,914 consecutive cases of hysterectomy. In 1919, W. H. Weir adopted the pan- or total hysterectomy as the procedure of choice, and since then the proportion of this type of operation has steadily increased. The technique<sup>3</sup> is a simplified modification of previously described operations.

As seen in Table I, this operation now constitutes almost 75 per cent of all hysterectomies. The supravaginal hysterectomy is, as a rule, done by the resident staff only when complications are so extensive that pan-hysterectomy cannot be done with safety. The number of vaginal hysterectomies is low because this procedure is usually reserved for those patients with at least a second-degree prolapse. The proportion of white to colored patients is the same in all groups except in vaginal hysterectomy in which it is interesting to note the very small incidence of this operation in colored people, due to their seldom having prolapse. The majority of parous patients fall into the pan- and vaginal hysterectomy groups, particularly the latter, where prolapse is almost invariably a result of birth trauma. In the supravaginal group, slightly less than one-half are nulliparous. The explanation for this is plain when one realizes that the cervix is more liable to be normal in the nulliparous patient and the frequency of salpingitis in this group with resulting complications makes panhysterectomy difficult in a larger number.

The age distribution of this series is shown in Table II. The majority of cases fall into the fourth and fifth decades of life at, or near, the time of the menopause when symptoms of pelvic lesions may become most

diate preliminary to hysterectomy. The repair of a relaxed pelvic floor as an additional pelvic support following hysterectomy is felt in this clinic to be essential. Because the posterior relaxations are the most frequent, the perineorrhaphies closely parallel the occurrence of childbirth in these patients. The incidence of appendectomy is high, because it is done routinely except when the condition of the patient or the difficulties in removal of the appendix contraindicate the procedure. Primary disease in the adnexa and incidental pathologic conditions necessitating partial or complete removal of the adnexa are frequently found. Ovaries are always saved when possible. Cholecystectomy in addition to pelvic work was done on ten occasions by one operator, but this combination operation is usually felt to be too hazardous.

Injuries to the ureters, bladder, and bowel are one of the chief worries of the operator. However, consciousness of these dangers has kept the number extremely low as shown in Table VI. It should be noted that the incidence was no greater in the panhysterectomies than in the supravaginal hysterectomies.

The various common postoperative complications are enumerated in Table VII. In spite of the fact that the majority of cases are clean, the number of infected wounds, although not great, is perhaps more than it should be. We hope closer attention to hemostasis and pre-operative preparation will help in correcting this. Six of the 11 patients with peritonitis died. None could be attributed to removal of the appendix. Seven of the 15 cases of pulmonary embolus were fatal. The high incidence of cystitis is due to the necessity of traumatizing the bladder somewhat at operation. However, work is now being done on

TABLE VI. OPERATIVE COMPLICATIONS

	130 VAGINAL HYSTEREC- TOMY		348 SUPRAVAGINAL HYSTEREC- TOMY		1,436 PANHYS- TEREC- TOMY		1,914 TOTAL	
			NO.	%	NO.	%	NO.	%
Cut ureter			1	0.28	3	0.21	4	0.21
Torn bladder			2	0.57	10	0.69	12	0.63
Torn bowel			2	0.57	7	0.48	9	0.47

TABLE VII. POSTOPERATIVE COMPLICATIONS

	130 VAGINAL HYSTEREC- TOMY		348 SUPRAVAGINAL HYSTEREC- TOMY		1,436 PANHYS- TEREC- TOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Infected wound			14	4.0	53	3.7	67	3.5
Peritonitis			4	1.15	7	0.49	11	0.57
Phlebitis			3	0.86	12	0.84	15	0.78
Fistula					6	0.41	6	0.31
Pulmonary embolus	2	1.54	2	0.57	11	0.77	15	0.78
Pyelitis	4	3.07			13	0.91	17	0.89
Cystitis	27	20.8	23	6.6	107	7.5	157	8.2
Pneumonia	2	1.54	8	2.3	13	0.91	23	1.2
Hemorrhage			3	0.86	11	0.77	14	0.73

removed. Relaxed vaginal outlet follows roughly the incidence of childbirth. The higher incidence of salpingitis in the supravaginal hysterectomy group is due to the complications resulting from this condition. The diagnosis of carcinoma of the cervix appears infrequently in this series due to the fact that the majority of these are treated with radium and x-ray. The 7 present were early cases treated by radical hysterectomy for teaching purposes or were undetected before operation. The incidence of prolapse is very high in the vaginal hysterectomy group, because this procedure is rarely performed in this clinic except for this condition.

In attempting to classify the number and types of symptoms for which hysterectomy is done, there is such a variation in number and degree that a true picture cannot be drawn. Table IV, is, therefore, at best only a rough determination from the information supplied by the patient and recorded in the history. Urinary symptoms have been omitted because of their variety and frequency and because they are mostly secondary. It is interesting that the symptoms are the same in the pan- and supravaginal hysterectomies.

Additional operative procedures at the time of hysterectomy are frequently either necessary or desirable. The incidence of these is shown in Table V. A dilatation and curettage is felt to be a diagnostic procedure in this clinic and should be done if necessary some time before the operation is decided upon. As a result, it is not often done as an imme-

TABLE IV. DISTRIBUTION OF MOST COMMON SYMPTOMS

	130 VAGINAL HYSTEREC- TOMY		348 SUPRAVAGINAL HYSTEREC- TOMY		1,436 PANHYS- TEREC- TOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Pain	66	50.7	234	67.2	964	67.1	1,264	66.1
Bleeding	13	10.0	139	40.0	624	42.5	776	40.5
Tumor			40	11.5	163	11.5	203	10.6
Prolapse	83	63.8	4	1.15	16	1.1	103	5.4

TABLE V. ADDITIONAL OPERATIVE PROCEDURES

	130 VAGINAL HYSTEREC- TOMY		348 SUPRAVAGINAL HYSTEREC- TOMY		1,436 PANHYS- TEREC- TOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Dilatation and curet- tage	1	0.8	65	18.6	79	5.5	146	7.6
Perineorrhaphy	125	96.2	95	27.2	898	62.5	1,118	58.4
Anterior colporrhaphy	83	63.8	18	5.2	257	17.9	358	18.7
Partial removal of adnexa	5	3.8	131	37.6	476	33.2	612	32.0
Complete removal of adnexa			85	24.4	262	18.2	347	18.1
Appendectomy (pos- sible)			194	71.3	928	64.5	1,122	58.1
Hemorrhoidectomy	10	7.7	12	3.4	96	6.7	118	6.2
Cholecystectomy					10	0.7	10	0.5

is very low. With the visiting staff, the results are even more remarkable. In the 531 cases, there was only one death, or a 0.18 per cent mortality. Combining both groups of panhysterectomies, there were 1,436 cases in all with a mortality rate of 0.767 per cent. The total mortality rate in 1,914 cases of all types of hysterectomies is 1.2 per cent.

In conclusion, statistics have been presented and briefly explained on a large number of consecutive hysterectomies, the majority of which were panhysterectomies. The extremely low mortality rate and the absence of increased operative and postoperative complications in the panhysterectomy group leads us to believe that, in properly trained hands, the operation involves no greater risks than the supravaginal hysterectomy and should be the one of choice when the uterus is to be removed.

## REFERENCES

- (1) Fullerton, W. D., and Faulkner, R. L.: *J. A. M. A.* 95: 1563, 1930. (2) Faulkner, R. L.: *Ohio State M. J.* 32: 229, 1936. (3) Weir, W. H.: *Trans. Am. Assn., Obst. Gynec. & Abd. Surg.* 44: 337, 1931.

## TATTOOING WITH MERCURIC SULFIDE FOR THE TREATMENT OF INTRACTABLE PRURITUS VULVAE AND ANI\*

### AN ANATOMICOCLINICAL STUDY

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## INTRODUCTION

**T**HERAPEUTIC tattooing with mercury sulfide and other chemicals has been used in the past for a variety of medical and surgical conditions.<sup>1</sup> Recently, this form of therapy has been successfully employed for the treatment of intractable pruritus ani,<sup>2-4</sup> and in selected cases of pruritus of leucoplakia-kraurosis vulvae.<sup>5</sup> Tattooing has proved to be of little value thus far in the treatment of pruritus vulvae of undetermined origin or with superimposed dermatitis. A satisfactory technique of tattooing of the vulva, comparable to that described for the tattooing of the perianal and anal regions<sup>1</sup> is in process of development. Difficulty has been encountered, especially in the tattooing of the clitoris and the surrounding cutaneous folds.

Preliminary investigations of the mechanism of the action of mercury sulfide deposited in the corium by tattooing point to functional impairment of the cutaneous sensory terminals with a resultant alteration in the capacity of this neural system to respond to adequate stimuli. Apparently, a change in the cutaneous modalities is produced which, within limits, is proportional to the amount of intracutaneous deposit of mercury sulfide.<sup>4</sup> The mechanical trauma alone produced by the tattoo-

\*Presented, by title, at a meeting of the American Federation for Clinical Research, Atlantic City, N. J., May 5, 1941.

better care of the bladder postoperatively to reduce the occurrence of cystitis. It should be noted again that the number of complications is approximately the same in the pan- and supravaginal hysterectomies.

The postoperative morbidity, Table VIII, is determined by the number of days the patient's temperature reaches 38.5° C. or higher. The vaginal hysterectomies show a somewhat higher morbidity. It is also found to be higher in the supravaginal hysterectomies due to the increased number of operative complications in this group.

The mortality rates are shown in Table IX. The 4 deaths in the vaginal hysterectomies give a higher rate than in the other types of hysterectomies. These women were older and also poorer operative risks. The number of vaginal hysterectomy cases, however, is not sufficient to give an accurate mortality rate for this type of operation.

TABLE VIII. MORBIDITY

	130 VAGINAL HYSTEREC- TOMY		348 SUPRAVAGINAL HYSTEREC- TOMY		1,436 PANHYS- TEREC- TOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Temperature below 38.5° C.	55	42.3	150	43.1	702	48.9	907	47.4
Temperature above 38.5° C. for one day	29	22.3	59	16.9	399	21.5	397	20.7
Temperature above 38.5° C. for more than one day	46	35.4	139	40.0	425	29.6	610	31.9

TABLE IX. MORTALITY RATES

	130 VAGINAL HYSTEREC- TOMY		348 SUPRAVAGINAL HYSTEREC- TOMY		1,436 PANHYS- TEREC- TOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Resident Staff	2	2.48	7	5.88	10	1.10	19	1.72
Visiting Staff	2	4.08	1	0.43	1	0.188	4	0.49
Combined Staffs	4	3.08	8	2.30	11	0.767	23	1.2

A mortality rate of 5.88 per cent in the resident staff's series of supravaginal hysterectomies is undoubtedly high. However, this procedure is done only when panhysterectomy is found to be too difficult. The group, therefore, includes practically all the complicated cases and a higher rate is to be expected. The visiting staff tend to do more supravaginal hysterectomies proportionally, and their mortality rate of 0.43 per cent is low.

The resident staff did 905 panhysterectomies or slightly less than double the number done by the visiting staff. In this series, there were only 10 deaths, or 1.1 per cent. None of the members of the resident staff, except two who did 37 cases, had more than two years of experience in specialized gynecology. In spite of this inexperience, but because of the standardized and simplified technique, the mortality rate



Fig. 1, A.



Fig. 1, B.

Fig. 1.—Photomicrographs of sections of tattooed perineoperianal skin taken at various intervals of time (Case 1). *A*, Immediately after tattooing, showing perforations in the epidermis with considerable deposit of mercury sulfide in the epithelium and massive deposition in the upper corium. *B*, Three months later, showing a sub-epithelial deposit of clumps of mercury sulfide without evidence of foreign body giant cell reaction. At this stage most of the deposit of the chemical is in the upper corium with some of it in the middle corium. *C*, Six months after tattooing, showing a histologic picture similar to that of *B*. *D*, Ten months after tattoo, showing a histologic picture essentially the same as that observed in *B* and *C*.

ing machine without deposition of mercury sulfide<sup>4</sup> is ineffectual in producing permanent relief of the pruritus ani.

Although cutaneous syphilitic lesions apparently do not occur in the areas of skin that are tattooed with mercury sulfide,<sup>6-8</sup> convincing proof of the antiseptic value of intracutaneously deposited mercury sulfide in infections other than syphilis is still lacking. This is in agreement with Aoki.<sup>7</sup>

#### THE PRESENT STUDY

The work embodied in this paper deals with histologic studies of skin which had been tattooed with mercury sulfide as the treatment of intractable localized pruritus; particular reference was made to the fate of mercury sulfide deposited intracutaneously and to its possible effect on the skin.

Fractional skin biopsies were taken from the perineoperianal junction of a woman treated for intractable pruritus perinei and ani immediately after tattooing (Fig. 1, *A*), at three months (Fig. 1, *B*), six months (Fig. 1, *C*), and ten months (Fig. 1, *D*). Fig. 1, *A* shows many perforations in the epidermis by puncture holes with considerable deposit of mercury sulfide in the epithelium and massive deposition in the upper portion of the corium. No other significant changes are observed. Fig. 1, *B* shows a subepithelial deposit of clumps of mercury sulfide; at this stage most of the deposit is in the upper corium, with some of it in the middle portion of the corium. Infiltration of round cells is present without evidence of foreign body giant cell reaction. The epithelium appears normal. This corresponds to the clinical observation that desquamation of the tattooed epidermis occurs within a few days after treatment and that re-epithelization takes place within a few weeks. The histologic pictures seen in Figs. 1, *C* and *D* are essentially the same as that observed in Fig. 1, *B*.

Another patient had the entire vulva tattooed with mercury sulfide because of pruritus of undetermined origin. Six months after tattooing, a biopsy was performed and a specimen for histologic study was removed from the skin of the right side of the mons veneris. A biopsy of the skin of the opposite side of the mons was performed twelve months after tattooing. Like Figs. 1, *B*, *C*, and *D*, these sections show the deposit of clumps of mercury sulfide in the corium without evidence of foreign body giant cell reaction.

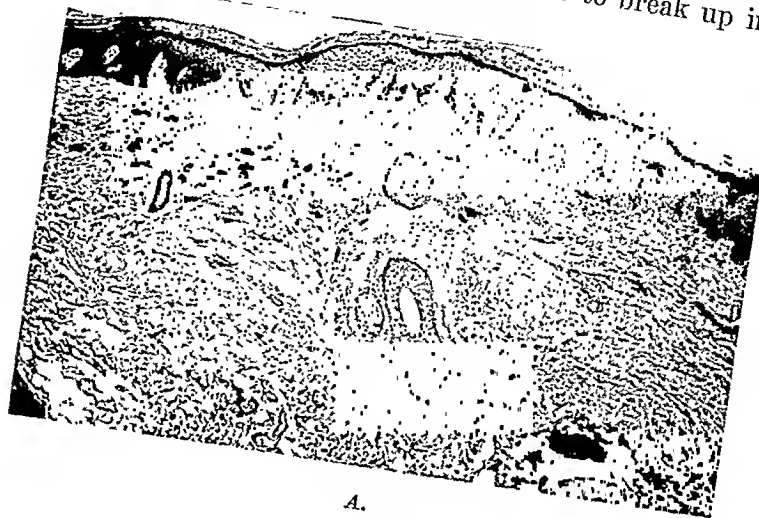
The third patient was a 60-year-old white woman, who had the perianal circumference, perineum, and the posterior portions of the labia majora tattooed with mercury sulfide in two stages (Aug. 11, and Sept. 1, 1939) because of intractable pruritus perinei and ani. The left perineoperianal region was incompletely tattooed with resultant skipped areas in which recurrence of mild intermittent pruritus developed. A study of the cutaneous modalities, while unsatisfactory because of the patient's poor cooperation, nevertheless revealed suggestive diminution of the painful and tactile sensations on the opposite perineoperianal side which had been adequately tattooed and which was free from any recurrence of pruritus. Biopsies of skin from each perineoperianal aspect were performed Aug. 16, 1940 (about one year after tattooing). The histologic examination of skin removed from the incompletely tattooed side in which some intermittent pruritus recurred showed areas that had either no mercury sulfide or an uneven scant deposit (Fig. 2, *A*). In contrast, the adequately tattooed skin of the opposite nonpruritic side of the same patient revealed a uniform and abundant subepithelial deposit of mercury sulfide (Fig. 2, *B*). Again, no evidence of foreign body giant cell reaction is discernible in these sections.

The fourth patient was tattooed with mercury sulfide because of distressing pruritus vulvae, perinei, and ani caused by leucoplakia-kraurosis; the pruritus had not been controlled by a previous partial vulvectomy and four subsequent surgical procedures.<sup>5</sup> It was noted that "one month after tattooing the skin about the

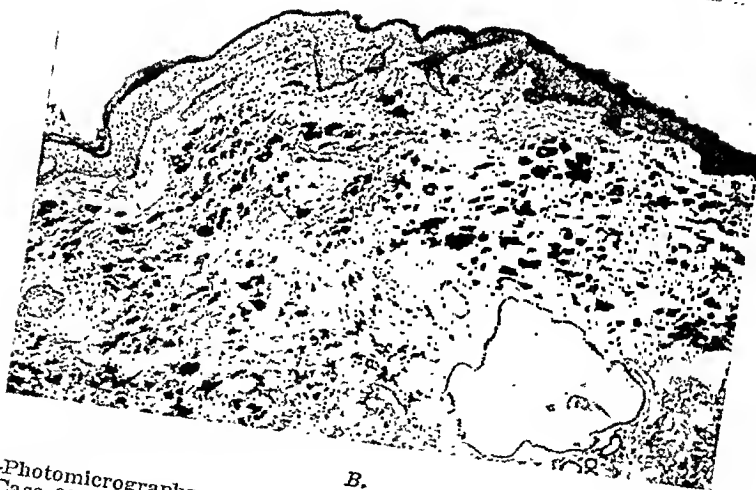


## COMMENT

The histologic studies of sections of skin taken immediately after tattooing show a homogeneous mass of mercury sulfide chiefly situated in the upper corium with some deposit in the epithelium. Later on, the chemical is localized in the corium and seems to break up into smaller



A.



B.

Fig. 2.—Photomicrographs of sections of perineoperianal skin taken one year after tattooing (Case 3). *A*, Section of skin from incompletely tattooed side, showing areas that have either no mercury sulfide or a scant deposit. There was recurrent pruritus on this side. *B*, Sections of skin from the opposite, adequately tattooed nonpruritic side, showing a uniform and abundant subepithelial deposit of mercury sulfide. Foreign body giant cell reaction is not discernible.

variously-sized clumps which have a slight but definite tendency to reach the deeper portion of the cutis (Figs. 1, *B*, *C*, and *D*). Unlike other foreign bodies introduced into the skin, mercury sulfide deposited intracutaneously by tattoo is not accompanied by a foreign body giant cell reaction.

introitus and in the perianal region, with the exception of the perineal area, was normal in appearance." Furthermore, eight months later the patient was still free from pruritus "in spite of the presence of moderate excoriation of the perineum"; this excoriation was believed to be caused by a continuous escape of vaginal discharge for which the patient refused treatment as she preferred to "leave things well enough alone." On July 26, 1940, about thirteen and one-half months later, the patient noted burning and pain in the perineum, especially after defecation. Examination revealed vaginal discharge and a grayish white perineum with three superficial fissures, of which one extended to the anal orifice. One week later, there occurred



Fig. 1, C.

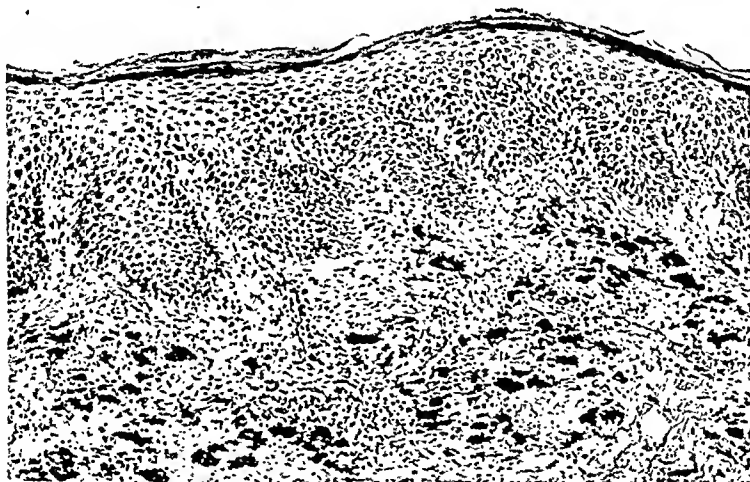


Fig. 1, D.

moderate pruritus confined only to the perineum. Biopsies of skin were taken from the perineum and from a well tattooed nonpruritic area, 2 cm. from the site of the perineal biopsy. The histologic examination of the perineum (Fig. 3, A) shows a scant deposit of mercury sulfide deep in the corium, many lymphocytes, and leucocytes. The section from a well-tattooed nonpruritic (control) area shows a uniform and an abundant subepithelial deposit of mercury sulfide, as well as moderate infiltration of round cells (Fig. 3, B). (The elastica stains of both sections also show fragmentation and degeneration of the elastic fibers.)

## SUMMARY

Histologic studies of skin biopsies of four selected patients tattooed with mercury sulfide for the treatment of intractable localized pruritus are presented. Massive deposition of the mercury sulfide in the upper portion of the corium with some deposit in the epithelium is seen immediately after adequate tattooing. Later on, the mercury sulfide is localized in the corium as clumps of various sizes, which have a slight but definite tendency to reach the deeper portion of the skin. Evidence of foreign body giant cell reaction in the skin commonly seen after the introduction of other foreign substances intraeutaneously has not been observed following tattooing with mercury sulfide. It appears that the quantity and the distribution of the mercury sulfide deposited intraeutaneously by tattoo can be correlated with its therapeutic effectiveness.

I am indebted to Dr. S. H. Geist for his assistance and encouragement in this work.

## REFERENCES

- (1) *Turell, R., and Marino, A. W. M.*: Ann. Surg. To be published. (2) *Hollander, E.*: Arch. Dermat. & Syph. 38: 337, 1938. (3) *Turell, R., Buda, A. M., and Marino, A. W. M.*: Arch. Dermat. & Syph. 41: 521, 1940. (4) *Turell, R.*: J. Invest. Dermat. 3: 289, 1940. (5) *Idem*: AM. J. OBST. & GYN. 40: 334, 1940. (6) *Dohi, S.*: Arch. f. Dermat. u. Syph. 96: 3, 1909. (7) *Aoki, T.*: Dermat. Ztschr. 19: 508, 1912. (8) *Belote, G. H.*: Arch. Dermat. & Syph. 18: 200, 1928.

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## SYPHILIS AND UNCONTROLLED FERTILITY

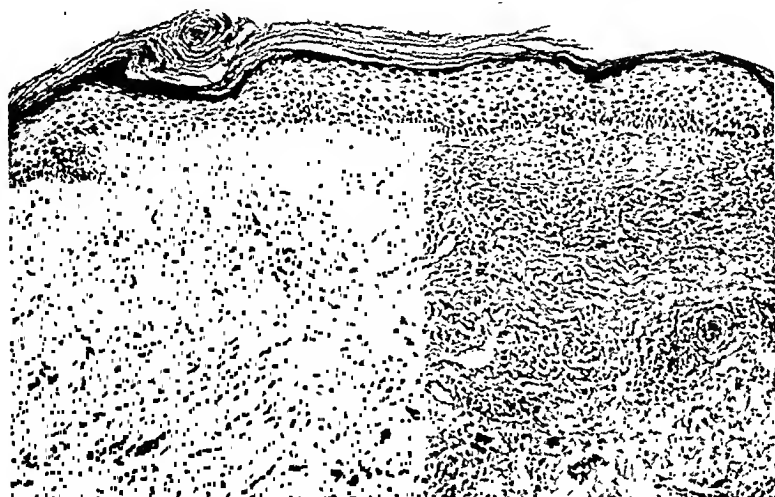
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(From the Milbank Memorial Fund)

RECENT studies have shown that the factors of greatest importance in determining differences in the fertility of large groups of women are those associated with voluntary attempts to control fertility by means of contraception and induced abortion.<sup>5, 8, 9, 11</sup> When the extent of these efforts is known and can be excluded from the experience of a group, it becomes possible to measure the effect of other factors on the uncontrolled fertility of the group.

In the course of a recent study of a group of indigent negro women from a cotton-mill area in the South, it was found that when no attempt had been made to control fertility by means of contraception or induced abortion, the pregnancy rates of women with syphilis, but free from gynecologic or endocrine pathology, were consistently and significantly lower than those of women free from syphilis as well as from the other types of pathology. This finding, so far as I have been able to ascertain, is a new one, and the records of the women under consideration were,

The histologic studies show that the quantity and distribution of the mercury sulfide in the skin can be correlated with its therapeutic effectiveness. For example, a scant subepithelial deposit of mercury sulfide as seen in Fig. 2, *A* is discernible in the skin of the incompletely



A.



B.

Fig. 3.—Photomicrographs of sections of skin removed thirteen and one-half months after tattooing. *A*, Section of skin from perineum (site of recurrence of pruritus), showing scant deposit of mercury sulfide deep in the corium, many leucocytes, and lymphocytes (see text). *B*, Section of skin from well-tattooed nonpruritic (control) area, showing uniform and an abundant subepithelial deposit of mercury sulfide, and moderate infiltration of round cells. Again note the absence of foreign body giant cell reaction.

tattooed anoperineal region which was the site of recurrent, localized areal pruritus. In contrast, the opposite, nonpruritic, adequately-treated anoperineal site of the same patient shows an abundance of mercury sulfide well distributed (Fig. 2, *B*). This is consistent with the clinical observations made previously.<sup>4</sup>

accepted in the Maternal Health Clinic. Each record, therefore, included a digest of the medical history and diagnosis, as well as reports of laboratory tests. At the Maternal Health Clinic each woman was given a complete pelvic examination.

The record of each patient contained a fertility history which included the date and type of termination of each pregnancy and information concerning the use of contraception, if any, which preceded it. The women were also questioned about the length of lactation following each live birth and of post-partum amenorrhea following each delivery.

The patients were classified into three groups: (1) women whose records showed no evidence of inflammatory conditions in the pelvis, of endocrine disease, of pellagra, or of syphilis; this will be designated hereinafter as the "nonpathologic" group; (2) women with any evidence of pelvic inflammation, of endocrine pathology, or of pellagra, including those who had syphilis in addition to the other types of pathology; and (3) women who had positive Wassermann reactions and/or a diagnosis of syphilis or a history of syphilis but had no other disease which might be presumed to affect their fertility. For the purposes of the present study we are concerned only with the first and third groups.

In order to eliminate the possible influence of pelvic pathology, following gonorrheal or other pelvic infection, on the fertility of the women under consideration, all women with definite evidence of pelvic inflammation or with positive smears for gonorrhea were excluded from the two samples selected for study. The pelvic findings for women with no evidence of disease and for women with syphilis only are compared in Table I.

TABLE I. PROPORTIONS OF NEGRO WOMEN WITH AND WITHOUT SYPHILIS WHO HAD CERTAIN TYPES OF PELVIC PATHOLOGY

TYPE OF PATHOLOGY	WOMEN WITHOUT PATHOLOGY WHICH MIGHT BE EXPECTED TO AFFECT FERTILITY	WOMEN WITH SYPHILIS BUT FREE FROM SERIOUS PELVIC OR ENDOCRINE PATHOLOGY
	NUMBER OF WOMEN EXAMINED*	
	241	111
	PER CENT WITH EACH TYPE OF PATHOLOGY	
Cervix lacerated (no inflammation)	78.6	75.7
Cervix lacerated and inflamed	14.3	13.5
Cervix inflamed (no laceration)	1.3	1.8
Uterus retroflexed and/or retroverted	63.9	58.9
Uterine masses and/or tenderness	0.4	1.9
One or both tubes tender and/or painful	2.1	4.5
One or both ovaries tender and/or painful	2.5	3.6
Smear positive for gonorrhea	0.0	0.0
Smear doubtful for gonorrhea	1.3	1.9

\*The number of women in each group who had complete pelvic examinations was less than the number shown. In each instance the proportion shown is based on the number for whom the specific organ was examined.

The prevalence of cervical inflammation and pain and/or tenderness of the uterus and adnexa was low in both groups. It was slightly but not significantly higher for the syphilitic women than for the nonpathological group. Malposition of the uterus, on the other hand, was slightly more prevalent among the women free from pathology. The data in

therefore, subjected to detailed analysis, in order to determine, if possible, the reasons for the relatively low uncontrolled fertility of the syphilitic women.

Little is known about the effect of syphilis on uncontrolled fertility.

White and Veeder stated, in 1922, that: "Syphilis in the parents may react upon the succeeding generation in several ways: first, by preventing or inhibiting pregnancy; second, by causing the death of the unborn child; third, by being transmitted to the living child while yet in utero."<sup>14</sup>

Numerous studies have shown that there is a high fetal mortality among the pregnancies of syphilitic women. A few students of the problem have reported a large proportion of childless couples among syphilitic families, but no attempt has been made to determine whether the childlessness was voluntary or was attributable to the syphilis or associated pathology.<sup>7</sup> Physicians treating syphilitic couples would doubtless have advised them to use contraceptive measures both for prophylaxis of the disease and to prevent pregnancy, and it is therefore probable that many of the childless syphilitic couples were childless because of their use of contraceptives.

In studying the records of a group of negro women referred to the Spartanburg (South Carolina) Maternal Health Clinic for contraceptive advice, it was possible to isolate their experience without contraceptives, before they attended the clinic, and to study the association between syphilis and uncontrolled fertility for this group. The result of a blood test for syphilis was entered on the clinic record of every patient. It was found that 25 per cent of the negro women referred to the contraceptive clinic in the years 1935 to 1939 had three- or four-plus Wassermann and/or Kahn reactions, and an additional 6 per cent had one- or two-plus reactions.\* The number of records was large enough to permit of separate study of the fertility of the syphilitic women and of factors other than syphilis which might be expected to influence it.

#### THE DATA

Four hundred fifty-seven negro women were examined and advised at the Spartanburg Maternal Health Clinic during the period of study. About 60 per cent of them were the wives of unskilled or semiskilled workers in Spartanburg or in the cotton mills in the County. The remainder were wives of farm tenants, sharecroppers, or farm laborers. All came from families who were indigent or had very low incomes. Seventy-five per cent of them had made no attempt to practice contraception before they attended the Maternal Health Clinic. They were a highly fertile group, and had averaged 3.5 live births per woman, although their mean length of marriage prior to clinic attendance was only about eight years.

The Maternal Health Clinic is an intramural clinic in the Spartanburg General Hospital, run by the County Health Department. Each woman advised in the contraceptive clinic was referred directly from another hospital service or was examined in the medical clinic before she was

\*In a study of a negro population of a rural county in Tennessee, Crabtree and Bishop<sup>2</sup> found that 32.6 per cent of the negroes, 15-65 years of age, had positive Wassermann reactions.

TABLE II. DISTRIBUTION OF PREGNANCY TERMINATIONS FOR NEGRO WOMEN WITH AND WITHOUT SYPHILIS IN THREE AREAS

SOURCE OF MATERIAL AND YEAR OF SURVEY	PERCENTAGE OF PREGNANCY TERMINATIONS OF EACH TYPE							NUMBER OF PREG- NANCIES
	TOTAL	LIVE BIRTHS	NONVOLUNTARY PREGNANCY WASTAGE				IL- LEGAL ABOR- TIONS	
			TOTAL	STILL- BIRTHS	SPON- TANE- OUS ABOR- TIONS	THERA- PEUTIC ABOR- TIONS		
<i>Women With Syphilis</i>								
Spartanburg County, South Carolina, 1935-1939*	100.0	73.4	25.7	11.2	14.5	0.0	0.9	447
New York, New York, 1923**	99.9	79.1	20.9†					737
Tipton County, Tennessee, 1930†	100.0	72.9	27.1	8.9	18.2§			859
<i>Women Free From Syphilis</i>								
Spartanburg County, South Carolina, 1935-1939*	100.0	86.9	13.1	3.9	8.9	0.2	0.1	1,446
New York, New York, 1923**	100.0	94.9	5.1†					948
Tipton County, Tennessee, 1930†	100.0	96.7	3.3	0.4	2.9§			243

\*The figures relate to all pregnancies, including those occurring when contraception was used. The distribution of terminations of pregnancies occurring during exposures without contraception did not differ significantly from the distribution of total pregnancies.

\*\*Health Work for Mothers and Children in a Colored Community. New York Association for Improving the Condition of the Poor. Publication 131, 1924, Tables VIII and IX.

†Crabtree, James A., and Bishop, E. L.: Syphilis in a Rural Negro Population in Tennessee, Am. J. Public Health 22: 157-162, 1932, Table V.

‡Includes all abortions and stillbirths.

§All abortions.

"average" woman with syphilis in the Spartanburg group would have had only 13 pregnancies in the same period during which the woman without pathology would have had 15. Fig. 2 and Table III show the pregnancy rates per 100 years of exposure to the risk of pregnancy for the entire preclinic experience without contraceptives of these two groups of women.\*

The rates shown in Fig. 2 and Table III are derived from the total preclinic experience of the syphilitic and of the nonpathologic groups. Because of the possibility of bias inherent in this use of the data (see footnote p. 299) rates were computed separately for experience falling within a five-year period preceding the initial clinic contact. The rates for the period were 80 pregnancies per 100 years of exposure to risk

\*The concept of exposure to the risk of pregnancy is based on the assumption that women are exposed to the risk of becoming pregnant for that part of the period between menarche and menopause during which they are habitually having coitus, as in the marital state, and are not pregnant or in the puerperium. The length of exposure for each woman is computed by deducting from the total number of months between marriage and the date of record ten months for each full-term birth and a month in addition to the reported period of gestation for each abortion or premature birth, as well as all periods of abstinence or separation of husband and wife. Pregnancy rates are then derived by summing the pregnancies and the total number of years of exposure of the group and dividing the number of pregnancies by the number of years of exposure to risk. The quotient is then multiplied by 100 in order to have a rate expressed in whole numbers. For further details, see Stix and Notestein,<sup>11</sup> Appendix III.

Table I show quite clearly that differences in the prevalence of pelvic pathology were not great enough to account for differences in the fertility of the two groups.

Pregnancy and birth rates were computed separately for exposures without contraception for each of the groups under consideration.\* On the basis of these pregnancy and birth rates, it was estimated that a theoretical woman whose uncontrolled fertility represented the average of that exhibited by the nonpathologic group, who was married at fifteen and who used no contraception until she entered the menopause at forty-five, would have had 15 pregnancies, terminating in 13 live births during the thirty fertile years of her married life.† The "average" woman with syphilis would have had only 13 pregnancies and 10 live births in a similar thirty-year period. These figures show quite graphically that syphilis was associated with a reduction in uncontrolled fertility in this group; that women with syphilis not only conceived less rapidly than women free from pathology, but that their birth rate was much lower because of the higher rate of fetal mortality in syphilis. The difference in the number of live births expected in the syphilitic as compared with the nonpathologic families is small in terms of expected size of family, but actually represents a reduction of 23 per cent in effective fertility.

It has been shown that the relatively low birth rate of the syphilitic women was to some extent attributable to the high fetal mortality in syphilitic pregnancies. The distributions of pregnancy terminations for the Spartanburg negroes, with and without syphilis, are compared with those for similarly selected groups of negro women in two other areas in Table II.‡ The proportion of pregnancies terminating in stillbirths and abortions was very much higher in the syphilitic than in the nonsyphilitic groups (Fig. 1).

About 50 per cent of the syphilitic women who attended the Spartanburg Clinic had each had at least one abortion or stillbirth. On the other hand, only 29 per cent of the women free from pathology had had any abortions or stillbirths. Solomon and Solomon reported that, among syphilitic families in which the wife had a positive Wassermann reaction, 52.2 per cent of the women who had had any pregnancies had had one or more stillbirths or abortions. In the families in which only the husband's Wassermann reaction was positive, only 20 per cent had had any abortions or stillbirths.§

Pregnancy wastage, though important, is only one factor in the decreased fertility of women with syphilis. It has been shown that the

\*It must be borne in mind that the information on the fertility of the women studied was in the form of a history covering a period antedating the initial contact with the Maternal Health Clinic by lengths of time varying from one month to more than twenty years. The information concerning the Wassermann or Kahn reaction related only to the date of examination, which coincided with the initial clinic contact. To the extent that some women in the "nonpathologic" group may have had syphilis and recovered from it, and that some women in the "syphilis" group may have acquired syphilis late in their married life, the records probably do not represent the total experience of groups continuously free of pathology or continuously infected with syphilis. The presumptive presence of a few cases of healed syphilis in the "nonpathologic" group and of periods free of syphilis in the experience of the "syphilitic" group would to some extent minimize any differences in fertility attributable to the presence of syphilis.

†For the method of computing these theoretical rates, see Stix and Notestein,<sup>11</sup> pp. 32, 33, and Table 10.

‡The pregnancy wastage reported for the nonsyphilitic women in New York and Tennessee appears to be low, and there may have been some under-reporting of abortions and stillbirths in these groups. For comparable figures from studies of white women, see Stix and Notestein,<sup>11</sup> Tables 30 and 31; Stix and Wiehl,<sup>12</sup> Table I; and Wiehl,<sup>13</sup> Table II.

§Solomon and Solomon,<sup>7</sup> 1922, Table 30. The latter figure was derived from data presented in the table.



TABLE III. PREGNANCY RATES FOR NEGRO WOMEN WITH AND WITHOUT SYPHILIS WHEN NO ATTEMPT WAS MADE TO USE CONTRACEPTION

PERIOD OF MARRIED LIFE*	WOMEN WITH SYPHILIS, BUT FREE FROM OTHER TYPES OF PATHOLOGY	WOMEN FREE FROM SYPHILIS AND PELVIC OR ENDOCRINE PATHOLOGY		
	PREGNANCIES PER 100 YEARS OF EXPOSURE TO THE RISK OF PREGNANCY			
First pregnancy	116	203		
All later pregnancies:				
Total	74	91		
(Years since marriage)				
0- 4	81	99		
5- 9	77	91		
10-14	56	75		
15-29	64	76		
	NUMBER OF YEARS OF EXPOSURE AND NUMBER OF PREGNANCIES			
	EXPOSURE IN YEARS	NUMBER OF PREGNANCIES	EXPOSURE IN YEARS	NUMBER OF PREGNANCIES
First pregnancy	73.1	85	93.4	190
All later pregnancies:				
Total	373.2	277	775.8	709
(Years since marriage)				
0- 4	161.1	130	360.4	358
5- 9	126.3	97	245.8	223
10-14	62.2	35	113.2	85
15-29	23.5	15	56.4	43

\*A few women in the group were unmarried, and a number of others had premarital pregnancies. Whenever the information was available, exposure was computed from the date of first coitus. Where information concerning premarital experience was not available, the pregnancies for which exposure was unknown were excluded from the tabulations.

Both types of tabulation demonstrate clearly that the rates of the women with syphilis were consistently and significantly lower than the rates of the women without pathology. In other words, the women with syphilis conceived less rapidly than the women without pathology when both groups made no attempt to control conception. In the case of first pregnancies, 64 per cent of the women without demonstrable pathology conceived within three months of marriage, while only about 50 per cent of the women with syphilis conceived within that period. The low rates of the syphilitic women, after the first pregnancy, were not associated with longer periods of post-partum amenorrhea than those reported by the nonpathologic group. In fact, only about 25 per cent of the non-contraceptive exposure of the syphilitic group, as compared with 38 per cent of the exposure of the nonpathologic group, coincided with periods of amenorrhea. The large proportion of stillbirths and abortions among the pregnancies of syphilitic women probably accounted for this situation. These figures show that increased post-partum amenorrhea was not a factor in the low fertility of the syphilitic women.

#### COMMENT

It is difficult to determine just what factors were involved in the reduced fertility of the couples with syphilis. It is possible that at least part of the reduction may have been due to early, undetected and unreported abortion. It is also possible that the husbands of the syphilitic women may have been responsible to some extent for their low fertility.

for syphilitic women and 131 pregnancies per 100 years of exposure for women without pathology. These rates showed a greater difference than those for the total preclinic experience, for which the corresponding rates were 80 and 108.\*

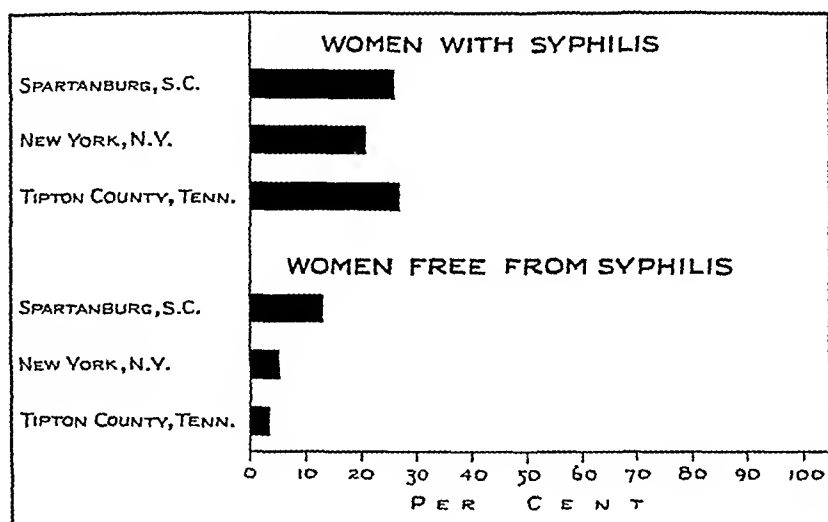


Fig. 1.—Percentage of pregnancies terminating in stillbirths and abortions for negro women with and without syphilis in three areas.

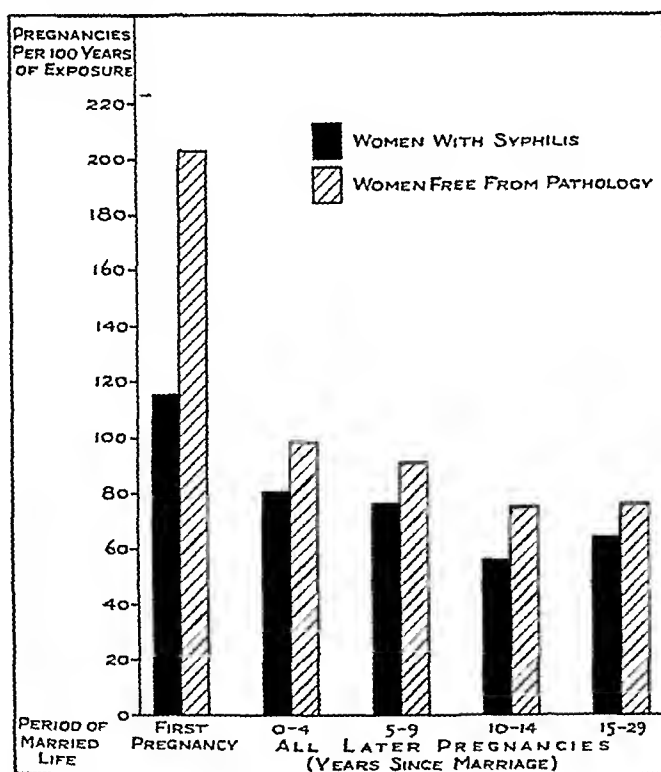


Fig. 2.—Pregnancy rates for negro women with and without syphilis, when no contraception was used.

\*Both sets of rates were standardized to the period-of-married-life distribution of the combined exposures of the two groups of women for the five-year period immediately preceding attendance at the clinic.

# ADENOCARCINOMA OF THE VULVA

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**C**ARCINOMA of the vulva is not a rare disease. The majority of carcinomas in this region are naturally of the squamous cell type. Adenocarcinomas are much rarer. The glandular structures which normally are present in the vulva are sweat glands and mucus glands which form the gland of Bartholin. Sweat glands are numerous in the vulva and are of two types, the ordinary or eccrine and the exocrine or apocrine type. Occasionally, other glandular elements are found in the vulva in the nature of accessory breast tissue and remnants of the Wolffian ducts.

Several types of glandular neoplasms in the vulva have been described. The commonest type of glandular neoplasm is that which is described in the German literature as "hidradenoma vulvae." Pick applied this term in 1904 to certain adenomas of the vulva. He was able to trace the connection between these tumors and sweat glands, but expressed the opinion that they originate from rudimentary rather than normal sweat glands. Similar cases have been reported by Hoeck, by Blau, and by Woringen. Burg, in 1930, was able to find reports of 15 cases of hidradenoma in the literature, to which he added one. All except 2 cases were considered as benign. Eichenberg, in 1934, described 12 papillary adenomas of the vulva, all of which belonged in the group of hidradenomas. In addition to these cases which he believed were benign, he described one case which he interpreted as showing malignant changes. He considered that all these neoplasms had originated from sweat glands. Folsome, in 1940, expressed the opinion that 27 per cent of these neoplasms were malignant.

Other types of glandular neoplasms in the vulva have been described. A case of adenocarcinoma of the vulva was described by Greene in 1936, associated with a squamous cell carcinoma of the vulva in which the adenocarcinoma was thought to have arisen from aberrant breast tissue. Fossel, in 1935, described a case of cylindroma of the vulva.

## MATERIAL

Thirty-two tumors which had been removed from 31 patients are included in this study. These constituted all the primary adenocarcinomas of the vulva which had been removed at the Mayo Clinic from 1906 to 1939, inclusive. Since the majority of these tumors were small, microscopic sections could be made which included a cross section of the entire tumor. Histologic sections stained with hematoxylin and eosin were studied. Occasionally, special stains were utilized. The clinical records on these patients were reviewed, for the most part, independent of the histopathologic studies.

Thirty of the neoplasms were papillary adenocarcinomas, and because of this have been grouped together. One was a fairly malignant solid adenocarcinoma which did not appear to belong in the first group. Another was an adenocarcinoma which appeared to be of the cylindroma type.

It is known that few, if any, of the husbands were absolutely sterile, since only five of the syphilitic women had had no pregnancies. Three of these women had been married for less than a year, and the others for less than four years. It is possible, however, that in the group in which the wives had syphilis, the husbands may have had temporary periods of sterility due to gonorrheal infection, even though the wives showed no evidence of gonorrheal infection or its sequelae when they were examined at the clinic.

The reduction in fertility observed in the syphilitic group is small but significant. Further research is necessary to determine whether other groups with syphilis also exhibit relatively low uncontrolled fertility rates.

#### CONCLUSION

It has been shown that a group of negro women with positive Wassermann reactions not only had a higher rate of fetal loss than women who were free from syphilis, but also conceived less rapidly than women free from pathology, when no attempt was made to control their fertility. It must be borne in mind, however, that the "relatively low" uncontrolled fertility demonstrated for the syphilitic women under consideration was actually high in terms of potential family size. It is clear, therefore, that any reduction in uncontrolled fertility associated with the presence of syphilis, while it may serve to throw some light on the relatively low birth rates of some negro groups, is insufficient to warrant a change in the routine prescription of contraception for patients with active syphilis.

#### REFERENCES

- (1) *Cole, H. N., and others*: Ven. Dis. Inform. 15: 1934; Reprint 46, 25 pp.
- (2) *Crabtree, James A., and Bishop, E. L.*: Am. J. Public Health 22: 161, 1932.
- (3) *Health Work for Mothers and Children in a Colored Community*. New York, New York Association for Improving the Condition of the Poor, 1924, Publication 131, 15 pp.
- (4) *Jean, P. C.*: Am. J. Syph. 3: 114, 1919.
- (5) *Pearl, Raymond*: The Natural History of Population, New York, 1939, Oxford University Press, p. 244.
- (6) *Solomon, H. C., and Solomon, M. H.*: Social Hygiene 6: 469, 1920.
- (7) *Idem*: Syphilis of the Innocent, Washington, 1922, United States Interdepartmental Social Hygiene Board, pp. 47, 48, and 113.
- (8) *Stix, Regine K.*: Am. J. OBST. & GYN. 35: 571, 1938.
- (9) *Idem*: The Milbank Memorial Fund Quarterly 17: 69, 1939.
- (10) *Idem*: The Milbank Memorial Fund Quarterly 18: 239, 1940.
- (11) *Stix, Regine K., and Notestein, Frank W.*: Controlled Fertility, Baltimore, 1940, The Williams and Wilkins Company, p. 39.
- (12) *Stix, Regine K., and Wiehl, Dorothy G.*: Am. J. Public Health 18: 621, 1938.
- (13) *Stokes, John H.*: Modern Clinical Syphilology, Philadelphia and London, 1935, W. B. Saunders Co., 1400 pp.
- (14) *White, Park J., and Feeder, Borden*: Am. J. Syph. 6: 353, 1922.
- (15) *Widakowich, F.*: Semaine méd. 27: 633, 1920 (and abstract in J. A. M. A. 76: 414, 1921).
- (16) *Wiehl, Dorothy G.*: The Milbank Memorial Fund Quarterly 16: 80, 1938.
- (17) *Wile, Udo J.*: J. Cutan. Dis. 34: 645, 1916.

In 12 of the 30 neoplasms, it was possible to demonstrate, within the tumor, acini in which the papillary projections were very prominent and in which the cytoplasm of the cells was strikingly eosinophilic and granular (Figs. 1 and 2). In all 12 cases, this peculiar epithelium could be traced into cells whose cytoplasm was not eosinophilic and which were definitely carcinomatous. The appearance of these peculiar glands corresponds in practically every detail to that of apocrine sweat glands (Figs. 3 and 4).

In 2 additional cases, apocrine glands were demonstrable adjacent to the papillary adenocarcinoma but were not incorporated in the neoplasm. The remaining papillary carcinomas, except for the presence of apocrine sweat glands, corresponded in histologic detail to the others.

In no instance could any connection be demonstrated between the mucus glands which form the gland of Bartholin and the adenocarcinomas in this group. In every instance, the carcinoma was situated on the labium majus, and in the majority the carcinoma was situated anterior to the usual site of the gland of Bartholin.



Fig. 1.

Fig. 1.—Papillary adenocarcinoma. The transition between the clear cells of the apocrine sweat glands and the carcinoma cells can be seen (hematoxylin and eosin  $\times 65$ ).

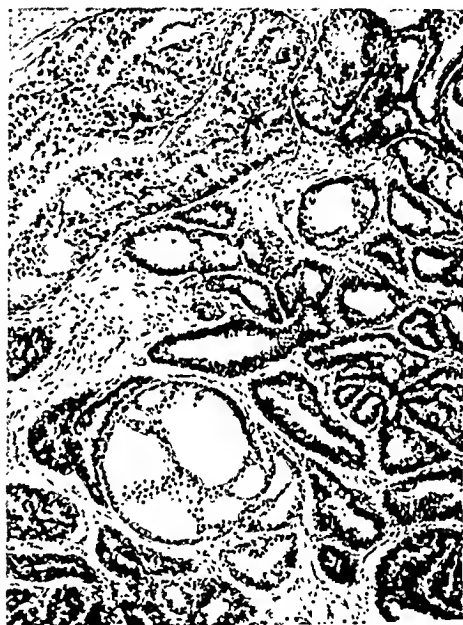


Fig. 2.

Fig. 2.—Papillary adenocarcinoma of the vulva. The epithelium of a portion of the tumor shows pale cytoplasm characteristic of apocrine sweat glands (hematoxylin and eosin  $\times 80$ ).

All papillary carcinomas which were small enough to localize in this group were situated in the corium immediately subjacent to the epidermis. As would be expected with a tumor in the corium, interference with the blood supply to the epidermis overlying the tumor occurred in several of these neoplasms with resulting ulceration of the epithelium.

*Miscellaneous Group.*—The two neoplasms in this group presented different histopathologic pictures. The first tumor was an adenocarcinoma with large irregular and very hyperchromatic nuclei in which mitotic figures were very abundant (Fig. 5). The metastatic growths in the lymph nodes presented an identical picture. This adenocarcinoma was Graded 3. The second tumor was an adenocarcinoma of the cylindroma type (Fig. 6). The cells were arranged in columns form-

## CLINICAL DATA

*Papillary Adenocarcinoma.*—The 30 neoplasms in this group were removed from 29 patients. Several of these neoplasms were unsuspected by the patient and were recognized only on physical examination. In the cases in which the tumor had been noticed by the patient, the tumor had been present in the majority of instances for many years. The usual clinical course was that the tumor had increased in size very slowly. Some tumors were not recognized by the patient or on physical examination, but were found and excised during the course of some perineal surgical procedure.

In several instances, the subjective symptom of pain was present because the surface epithelium over the tumor had ulcerated. The majority of these neoplasms were diagnosed clinically as sebaceous cysts, largely owing to the fact that many of these presented a cystic appearance.

In every instance except one, the tumor was confined to the labium majus. In one case, however, the lesion was fairly extensive, involving not only one labium but a portion of the vaginal wall and the perineal body. All of the remaining neoplasms measured 1 cm. in diameter or less.

None of the patients in this group were less than 32 years of age. The oldest patient was 67 years of age.

Excision of the tumor was sufficient in every instance to effect a cure. In most cases, a portion of the surrounding nonneoplastic tissue was removed with the tumor. In the one case in this group in which the tumor was extensive, excision by cautery of the affected vulva, vaginal wall, and perineal body resulted in a cure. The patient died sixteen years later from an unrelated condition, and up to the time of death there was no evidence of recurrence. Radium or roentgen therapy was not used in any case.

*Miscellaneous Adenocarcinomas.*—Two unrelated adenocarcinomas comprise this group. The only point of similarity is that neither one is papillary. The first tumor is an ordinary adenocarcinoma of a fairly malignant type and the second is an adenocarcinoma of the cylindroma type. The first adenocarcinoma was removed from a 22-year-old woman who had first noticed the tumor nine months previously. It had been excised elsewhere and roentgen therapy had been applied. On examination, the mass in the labium majus measured 4 cm. in diameter with involvement of the inguinal lymph nodes. Partial vulvectomy was performed together with bilateral dissection of the inguinal nodes. Postoperative roentgen therapy was completed. The patient died four months later.

The second adenocarcinoma, which was of the cylindroma type, was removed from a 36-year-old woman who had noticed a tumor in the posterior portion of the labium majus four years previously. There had been a gradual increase in size. Wide excision of the tumor was done, followed by radium and roentgen therapy. Seven years after this, a recurrent tumor was excised. Seven years after the second operation, the neoplasm apparently was arrested, although there was a small nodule in the old scar, the nature of which had not been determined.

## GROSS APPEARANCE

Approximately 60 per cent of the papillary adenocarcinomas were found within cysts. The remaining 40 per cent were solid. The two carcinomas belonging in the miscellaneous group were also solid.

## HISTOLOGIC APPEARANCE

*Papillary Adenocarcinomas.*—Well-formed acini were present in all the neoplasms in this group. In addition to the acini, papillary projections could be demonstrated readily in all these tumors. The nuclei were fairly large, slightly irregular, and hyperchromatic. Mitotic figures could be demonstrated but were scarce. All of these features are indicative of a slowly growing neoplasm. It is not surprising, then, that all of these carcinomas were Graded 1 or 2, using Broders' criteria. Twenty-eight of the 30 neoplasms in this group were Graded 1 and 2 were Graded 2.

In those specimens in which the tumor was found within a cyst, the neoplasm was attached at one or more points to the wall, often by a narrow stalk. The capsule of the cyst occasionally was invaded by the tumor cells.

ing poorly shaped acini. The individual cells were fairly small and had fairly regular nuclei. Mitotic figures were not numerous. This adenocarcinoma was Graded 1.

#### COMMENT

One can reasonably assume that practically all, if not all, papillary adenocarcinomas in the vulva are derived from apocrine sweat glands. This statement seems justified, since it has been shown that one-third of the papillary adenocarcinomas contained apocrine sweat glands. Additional support is offered by the fact that those papillary carcinomas which were small enough to localize were located in the corium of the vulva, which is the location of normal apocrine glands.

Several German authors have derived these neoplasms in the vulva from sweat glands. However, these authors did not derive these specifically from apocrine sweat glands, but rather from rudimentary sweat glands.

Apocrine sweat glands have been known for almost a century (Horner). These sweat glands, according to Homma, arise from the hair follicles. They are more numerous in negroes than in the white race. They are found in the axilla, in the perianal region, and around the perineum. Less commonly, they are found in other locations of the body such as the areola of the breast and the scalp. They are distributed widely in lower animals, according to Woollard. Whereas, the eccrine or exocrine glands secrete sweat without admixture of cell contents, the secretion from apocrine glands is formed by extrusion of a portion of the cytoplasm of the cell. Particularly in lower animals, the apocrine glands have a very definite function to perform in connection with sex instinct.

The similarity between these papillary adenocarcinomas of the vulva and intraductal papillary adenocarcinomas of the breast is evident. This is not surprising, since the breast is supposed to develop from apocrine sweat glands, according to some authorities.

The solid carcinoma of a higher grade of malignancy which metastasized seemed to represent a separate type of neoplasm; however, it is possible that this is of similar origin to the papillary carcinomas and that it is merely more malignant. This fact could not be proved.

The problem can be brought up as to whether these papillary neoplasms represent true carcinomas or not. Because of their histologic character, it would seem better to refer to them as adenocarcinomas of a low grade of malignancy rather than simple adenomas. Metastatic growths were not found in any of the cases of papillary carcinoma. However, it would appear probable that if a sufficient number of these cases were studied, metastatic growths would be found eventually.

From a practical standpoint it can be stated that because of the slow growth of the tumor and the slow tendency to metastasize, complete excision of the tumor together with a portion of the surrounding tissue is sufficient to effect a cure in these papillary carcinomas.

Adenocarcinomas of the cylindroma type are slow-growing neoplasms which are frequently difficult to eradicate because of local extension. The origin in this particular case of cylindroma could not be determined from the histopathologic studies. Montgomery and Kierland have been

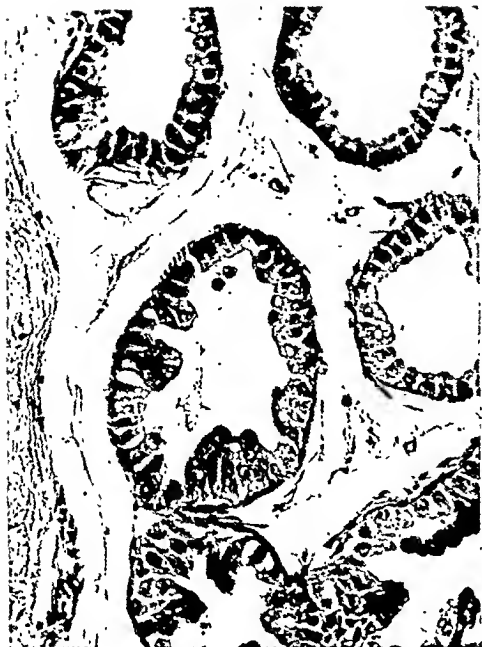


Fig. 3.

Fig. 3.—Apocrine sweat glands showing the two layers of cell and the characteristic papillary infoldings (hematoxylin and eosin  $\times 185$ ).



Fig. 4.

Fig. 4.—Apocrine sweat gland showing the close association with a hair follicle (hematoxylin and eosin  $\times 95$ ).

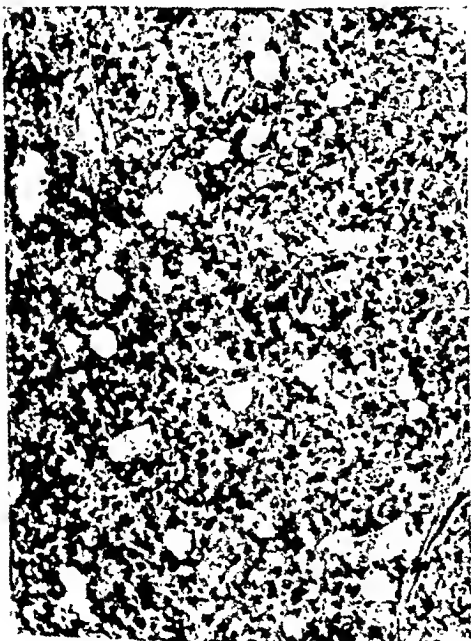


Fig. 5.

Fig. 5.—Adenocarcinoma of vulva. The neoplasm is not papillary (hematoxylin and eosin  $\times 155$ ).



Fig. 6.

Fig. 6.—Grade 1 adenocarcinoma of the cylindroma type (hematoxylin and eosin  $\times 85$ ).



and Mengert. Such tissue frequently was discovered during pregnancy because of its painful enlargement as a result of lactation. A fibroadenoma was reported in breast tissue in the vulva by Friedel in 1932.

Thirty-four neoplasms of the vulva were studied as the basis of this report. These represented tumors which had been removed from the vulva at the Mayo Clinic from 1906 to 1939 inclusive, specimens of which were available for study. The records of this series of cases were reviewed and pertinent details noted. Microscopic sections were studied; hematoxylin and eosin or any special stains which seemed indicated were employed. Endometriosis, accessory breast tissue, condylomas, epidermoid cysts and moles were not included because none except the last are true neoplasms. Moles were not included because of their common occurrence.

The 34 neoplasms presented 7 histologic types which included 16 fibromas, 7 lipomas, 5 hemangiomas, 2 neurofibromas, two leiomyomas, one ganglioneuroma, and one lymphangioma.

#### CLINICAL FEATURES

Lack of clinical symptoms in cases of benign tumors of the vulva was an outstanding feature. Many of the smaller tumors were not noticed by the patient but were discovered on routine physical examination. Some of the larger tumors caused mechanical difficulties. Pain occasionally was present, and in such cases ulceration of the epithelium overlying the tumor usually could be demonstrated. This ulceration can be explained readily on the basis of a decreased blood supply to the epithelium overlying the neoplasm. Many patients who noticed these tumors were worried concerning the possibility of malignant change in the tumor, because it had become larger over a period of years. In many cases, this was the sole factor which caused the patient to seek the services of a physician.

A study of the ages of the patients in this series did not reveal anything significant. The youngest patient was sixteen years of age and the oldest sixty-nine. Although the majority of patients were of childbearing age, 10 were more than fifty years of age.

#### PATHOLOGY

The 16 fibromas varied from 6 mm. to 8 cm. in diameter. The surface of several of the larger ones was ulcerated. Several different histologic pictures were found. The majority of tumors were made up of fairly adult fibroblasts which formed spindle cells. Mitotic figures were not demonstrated in any of the fibromas and myxomatous degeneration was a common finding (Fig. 1). Although several of the fibromas were cellular, none were considered sarcomatous. One patient related that the tumor had increased in size during two terms of pregnancy. Although a careful search of the specimen was made for breast tissue, none was found.

Seven lipomas were studied in this group. All represented single tumors in the vulva, but in one case, in addition to the single lipoma in the vulva, multiple lipomas were situated in the anterior abdominal wall. The most bulky tumors of any in this series were lipomas. One measured 17 cm. in diameter.

Because of the marked vascularity of the tissues of the vulva, it is not surprising that five of the tumors were hemangiomas. Because of the cavernous spaces normally found in the vulva, it was necessary to confine the diagnosis of hemangioma to a definite tumor composed of large, irregular, blood vascular spaces between which smooth muscle was not found (Fig. 2). The largest hemangioma measured 5 cm. in diameter. One was situated on the clitoris, the remainder on the labia majora. The surface epithelium of one hemangioma was ulcerated. The majority were of the cavernous type, exhibiting large blood spaces lined with a single layer of endothelium.

able to trace the connection between several of these tumors and the basal cells of the epidermis. They expressed the belief that they do not take their origin from sweat glands. Other authors derive these neoplasms from sweat glands, hair follicles, and sebaceous glands.

#### SUMMARY

Thirty-two adenocarcinomas of the vulva have been described. Of these, 30 were papillary carcinomas which originated from the apocrine sweat glands in this location. One was a nonpapillary adenocarcinoma and one an adenocarcinoma of the cylindroma type. The papillary carcinomas did not show a tendency to metastasize and were cured by simple excision of the neoplasm.

#### REFERENCES

- (1) *Blau, Albert*: Ztschr. f. Geburtsh. u. Gynäk. 93: 349, 1928. (2) *Burg, Ete*: Zentralbl. f. Gynäk. 54: 399, 1930. (3) *Eichenberg, Hans-Erich*: Ztschr. f. Geburtsh. u. Gynäk. 109: 373, 1934. (4) *Folsome, C. E.*: J. A. M. A. 114: 1503, 1940. (5) *Fossel, Max*: Zentralbl. f. allg. Path. u. path. Anat. 62: 153, 1935. (6) *Greene, H. J.*: AM. J. OBST. & GYNEC. 31: 663, 1936. (7) *Hoeck, Werner*: Zentralbl. f. Gynäk. 50: 2760, 1926. (8) *Homma, Hans*: Bull. Johns Hopkins Hosp. 38: 371, 1926. (9) *Horner, W. E.*: Am. J. M. Sc. 11: 16, 1846. (10) *Montgomery, Hamilton, and Kierland, R. R.*: Arch. Surg. 40: 684, 1940. (11) *Pick, Ludwig*: Virchows Arch. f. path. 175: 364, 1904. (12) *Woollard, H. H.*: J. Anat. 64: 421, 1930. (13) *Woringer, F.*: Bull. Soc. franç. de dermat. et syph. (Reunion dermat., Strasbourg) 45: 114, 1938.

### BENIGN TUMORS OF VULVA\*

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THE vulva includes the labia majora, labia minora, mons pubis, clitoris, and those structures contained in the labia, including the glands of Bartholin. Because of the variety of tissues in this region, benign neoplasms of the vulva are an interesting group.

Leonard, in 1917, pointed out that fibroma was the most common tumor of the vulva. He found 6 cases of fibroma of the vulva among 23,000 gynecologic cases at Johns Hopkins Hospital and reviewed 103 cases which had been reported in the literature to that time. The majority of these tumors were found during the childbearing age of the patient. Frequently, the tumor was found to enlarge during the period of menstrual flow. Leonard expressed the opinion that these tumors originated either from the connective tissue of the vulva or from the round ligament. Sarcomatous change was reported in 19 of the 103 cases. In 1929, Brady collected 175 cases of fibroma of the vulva from the literature.

In 1893, Kelly reviewed from the literature 20 cases of lipoma of the vulva. He pointed out that the lipomas were likely to simulate inguinal hernia. Endometriomas of the labia majora have been found in close connection with the round ligament. Such a case was reported by Jeffcoate in 1937. Accessory breast tissue has been reported in the vulva by several investigators, including Bell, McFarland

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## COMMENT

It is not surprising that benign tumors situated in the vulva produce so few symptoms. The vulva is a region of the body not seen by the patient; and swelling in this region does not in itself produce symp-

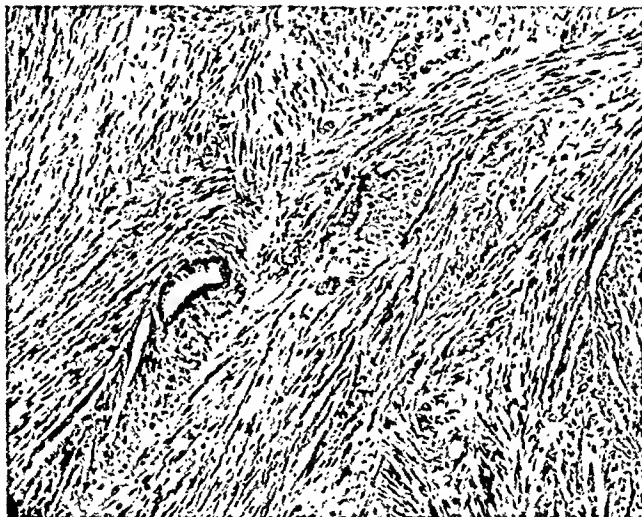


Fig. 3.—Leiomyoma of the vulva in which bundles of nonstriated muscle are evident (hematoxylin and eosin  $\times 80$ ).

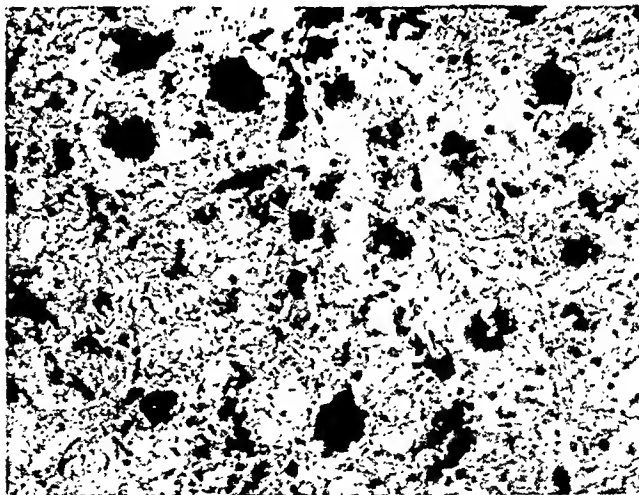


Fig. 4.—Ganglioneuroma of the vulva in which the ganglion cells are arranged in rosettes (hematoxylin and eosin  $\times 210$ ).

toms of pressure. Subjective symptoms were lacking except when ulceration of the epithelium occurred, in which case pain was caused by infection.

Evidence of sarcomatous change was not found in any of these neoplasms. This fact was apparent on histologic examination, and is further substantiated by the fact that in none of the cases in this series did the tumor recur.

The two leiomyomas encountered appeared grossly like leiomyomas of the uterus. The tumors were definitely encapsulated and one was lobulated. The whorling appearance of the cells, characteristic of leiomyoma, was evident. One tumor measured 6 by 3.5 by 3.5 cm., and the other measured approximately 4 cm. in diameter. Microscopically, both were composed of bundles of smooth muscle, with some fibrosis between the bundles (Fig. 3).



Fig. 1.—Fibroma of the vulva in which marked myxomatous degeneration can be seen (hematoxylin and eosin  $\times 80$ ).



Fig. 2.—Hemangioma of vulva in which large cavernous spaces can be seen (hematoxylin and eosin  $\times 80$ ).

The two neurofibromas were small; one measured 2 cm. in diameter and the other 1.5 cm. Pain was not a clinical feature in either case. On microscopic study, palisading of the nuclei could be seen. One neurofibroma was associated with a small cyst lined with squamous epithelium.

The ganglioneuroma included in this series measured 1.5 by 0.9 by 0.6 cm. Subjective symptoms were not produced by this lesion. The cells had prominent nucleoli and were arranged in the form of rosettes (Fig. 4). Nissl's bodies could be demonstrated in the cells when cresyl violet stain was employed.

One lymphangioma was demonstrated, which measured 7 mm. in diameter. Histologically, it consisted of a meshwork of lymphatic vessels.

## MYOMA OF THE VAGINA

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**M**YOMA\* arising from the vaginal wall is a rare condition and, since the first case was reported by Denys de Leyden<sup>1</sup> in 1733, not more than 200 authentic cases have been described in the literature. The condition is of interest because of its rarity and of importance because of the unusual problems which may arise in connection with its diagnosis. Because of the variety of sizes, appearances and locations of vaginal myomas, the condition has been variously mistaken for sarcoma,<sup>2</sup> carcinoma,<sup>3</sup> vaginal cyst (authors' Case 12), prolapsus uteri,<sup>4, 10</sup> cystocele,<sup>5, 6</sup> and adenomyoma of the vagina.<sup>7</sup> Notwithstanding the importance of this group of tumors in gynecologic diagnosis, little attention has been given the subject in textbooks of gynecology, and the only comprehensive reports appearing in the American or English literature were published by Phillips<sup>23</sup> in 1899, and by R. R. Smith<sup>8</sup> in 1902.

The subject was first reviewed by Kleinwächter<sup>9</sup> who, in 1882, reported 53 cases. Additional case reports and reviews were made by Phillips and Smith, and still others by Müller<sup>10</sup> and Stein.<sup>11</sup> Nürnberger<sup>12</sup> critically reviewed the literature in 1930 and considered only 130 cases of myoma of the vagina to be well authenticated. In contrast with this conservative estimate, Tourneux,<sup>1</sup> in 1934, accepted 160 cases reported by Potel<sup>13</sup> in 1903, and estimated that about 140 other satisfactory cases have since been recorded. Since Tourneux' review only occasional case reports have been published.

We have reviewed the material in the files of our laboratory for the past fifty years and have found 9 cases of primary myoma of the vagina, one of which (Case 1) has been reported previously by Kelly and Cullen.<sup>14</sup> We have been fortunate enough to obtain material and notes on three additional cases from the private files of T. S. Cullen, R. W. TeLinde, and Emil Novak. The important features of these twelve cases are presented below in tabular form (Table I) and discussed.

### INCIDENCE

The rarity of vaginal myomas is apparent when it is realized that only nine cases can be found in a gynecologic laboratory which contains more than 50,000 case specimens, including 19 cases of primary carcinoma of the vagina, 8 cases of primary sarcoma of the vagina and more than 100 vaginal cysts. A review of more than 15,000 autopsies performed in the Johns Hopkins Hospital reveals only one case of vaginal myoma. Similarly Piccagnoni<sup>15</sup> found only one case in 14,000 autopsy cases.

\*As pointed out by Kelly and Cullen<sup>14</sup> the term "myoma" has, in the case of the uterus, been used to include all fibromyomas, since pure myomas or pure fibromas are rarely if ever encountered. It is with this connotation that we use the term "myoma" in connection with fibroid neoplasms of the vagina.

The origin of the two leiomyomas in this group present an interesting problem. Smooth muscle is present in the vulva in the round ligament and erectile tissue. Each of these tumors was situated on the labium majus, too far posteriorly to have originated from the round ligament.

It is not surprising that hemangiomas and neurofibromas are found in the vulva because of the generous supply of blood vessels and nerves. The ganglioneuroma in this group is interesting only from a histopathologic standpoint, as it produced no subjective symptoms.

There is another group of tumors of the vulva which have been referred to in the literature as hidradenomas or tumors of the sweat gland. These neoplasms probably should be referred to as papillary adenocarcinomas rather than benign adenomas because of their histologic appearance and malignant potentialities. For these reasons, these tumors were not included in this series of benign neoplasms.

#### SUMMARY

Thirty-four benign neoplasms of the vulva encountered at the Mayo Clinic were studied. It was found that the commonest types of tumors were fibromas, lipomas, and hemangiomas, in the order named. Two neurofibromas, two leiomyomas, a ganglioneuroma and a lymphangioma also were encountered.

An outstanding feature was the lack of symptoms produced by the tumor in the majority of cases.

#### REFERENCES

- (1) *Bell, W. J.*: AM. J. OBST. & GYNEC. 11: 507, 1926. (2) *Brady, Leo*: Arch. Surg. 19: 1061, 1929. (3) *Friedel, R.*: Virchows Arch. f. path. Anat. 286: 62, 1932. (4) *Jeffcoate, T. N. A.*: Clin. J. 66: 206, 1937. (5) *Kelly, H. A.*: Johns Hopkins Hosp. Rep. 3: 321, 1893. (6) *Leonard, V. N.*: Bull. Johns Hopkins Hosp. 28: 373, 1917. (7) *McFarland, Joseph*: Arch. Path. 11: 236, 1931. (8) *Mengert, W. F.*: AM. J. OBST. & GYNEC. 29: 891, 1935.

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Brown, Preston T., and Pennington, John W.: Pelvic Symptoms of Urinary Tract Origin, J. A. M. A. 116: 189, 1941.

The authors stress the importance of ruling out urinary tract pathology in the diagnosis of the pelvic symptom complex. Genital diseases may be simulated by ureteral or urethral stricture, contracture of the vesical orifice, chronic urethritis and trigonitis, and rarely by ptosis of the kidney. Dysmenorrhea may be caused by ureteral stricture. A sensation of prolapse and pressure in the pelvis with actual descensus is strongly suggestive of some bladder or ureteral disorder. Urography, especially the intravenous method, is of vital importance in the diagnosis. Complete endoscopic examination and the determination of bladder capacity is also important. The authors conclude that it is the duty of the surgeon to make a careful and complete study of the urinary tract before ascribing obscure pelvic symptoms to uncomplicated retroversion, cystic ovaries, chronic cervicitis, or even more clear-cut forms of pelvic disease.

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*Age.*—In our series of 12 cases, the average age is 44 years, the oldest being 48 and the youngest 38. In the literature, however, vaginal myomas have been reported in patients from puberty to 71 years of age.<sup>18</sup> The average age, as in our cases, has been found to fall into the latter part of the childbearing period. "Fibromyomas" have been reported in infants,<sup>16, 17</sup> but microscopic evidence of myomatous elements is lacking in these cases, and it is possible that these lesions may simply have been papillomas.

*Color.*—In our series, 9 of 12 cases are white, and a majority of the reported vaginal myomas in the literature have been in white women. The racial incidence of vaginal myomas, therefore, contrasts strikingly with the racial incidence of uterine myomas which are almost three times as common in colored as in white women.<sup>14</sup> This fact we believe to be of particular interest in relation to the problem of etiology, and it will be discussed below.

*Marital Status.*—All of our 12 patients were married. In the literature, however, the reported cases show that vaginal myomas occur in married and unmarried, parous and nulliparous, women, alike, and there is no evidence to indicate that these conditions influence the incidence.

*Association with Uterine Myomas.*—A glance at our table of patients (Table I) shows that 6 of 12 cases had uterine myoma in addition to vaginal myoma. In 5 of these the uterine condition was proved at operation and confirmed by histologic study. In the sixth case (Case 1 in Table I) the uterus was studied at autopsy. The high incidence of uterine myomas in this series of vaginal myomas is at variance with previous observations recorded in the literature. Of the 130 cases of vaginal myomas reviewed by Nürnbergger,<sup>18</sup> only 10 were found to have associated fibroid tumors of the uterus. It is possible that uterine myomas may have been overlooked in certain of the previously reported cases.

#### PHYSICAL FINDINGS

*Gross Appearance.*—In 10 of our cases the vaginal myoma presented in the vagina as a nonpedunculated ovoid mass covered with smooth, intact mucosa and had no characteristic appearance such as would allow differentiation from a vaginal cyst, cystocele, or urethrocele. In 2 cases, the myoma was pedunculated, and these, too, were covered with normal mucosa.

In a number of reported cases, ulceration of the overlying mucosa has been noted with subsequent necrosis, purulent discharge and bleeding. In a case reported by Knauer,<sup>3</sup> the surface of a vaginal myoma the size of a "hen's egg" was ulcerated, necrotic, and bled easily, leading to a clinical diagnosis of carcinoma. Microscopic study after removal revealed the tumor to be a benign myoma.

Dicke<sup>19</sup> described a case in which the myoma protruded from the vulva and resembled a prolapsed uterus.

*Size.*—The vaginal myomas in our series are relatively small, varying from 1.5 cm. to 4.5 cm. in greatest diameter. These tumors may, however, reach tremendous size. Pistuddi<sup>20</sup> described a case with a vaginal myoma which after removal was found to weigh 1,450 Gm. Simon<sup>21</sup> observed a vaginal myoma the size of a "child's head," as did Hofmokl.<sup>22</sup> Phillips<sup>23</sup> recorded a case in which the removed tumor measured 5 by 3.5 inches.

*Number.*—In all of our cases, the lesion was a single myoma, but cases of multiple myomas in the vagina have been described. Olin and Torggler<sup>24</sup> reported a patient with multiple vaginal tumors which they believed to be myomas, but, according to Nürnbergger,<sup>24</sup> the microscopic findings suggested sarcoma. In 1934 A. F. Tyler<sup>25</sup> reported the case of a white woman, aged 68 years, with multiple myomas of the vagina, and these were diagnosed by biopsy and microscopic study.

*Site.*—Myomas may develop at any point in the vaginal wall. In 5 of our cases, the tumor arose in the anterior wall, in 4 the posterior wall, and in 2 the left lateral wall. In the remaining case, information as to location was lacking. In 5 cases, the myoma was in the posterior third of the vagina, and in 5 cases the anterior third. Of this latter group 4 were in the anterior wall near the midline and superficially resembled cystocele or urethrocele. In general, more than one-half of the tumors reported have occurred in the anterior wall, and about one-fourth in the

TABLE I. TABULATION OF CASES

CASE	GYNEC. PATIL. NO.	RACE	AGE	CIVIL STATUS	PARA.	POSITION	SIZE	SHAPE	CONSISTENCY	MUCOSA	UTERUS
1	353 (Autopsy)	C.	38	M.	0	Post. wall	4 x 2 cm.	-	-	-	Multiple "large," myomas
2	2597	W.	41	M.	ii	Post. to cervix	Small	-	"Hard,"	-	Normal
3	8259	W.	45	M.	-	Ant. wall	1½ x 1 cm.	-	"Hard,"	Intact	Normal
4	9070	W.	48	M.	i	Left lat. wall	Small	-	-	Normal	Normal
5	9877	C.	47	M.	iii	Left lat. wall, post.	1½ cm.	-	"Solid,"	-	"Slightly en- larged,"
6	14661	W.	43	M.	ii	Left lat. wall, post.	1½ cm.	Oval	"Solid,"	-	Myomas of uterus (12 x 11 x 9 cm.)
7	30867	W.	39	M.	-	Ant. wall	1½ in.	-	"Firm,"	-	Myomas of uterus
8	37957	W.	46	M.	-	Post. wall	"Lemon size"	Oval	"Solid,"	-	Myomas of uterus
9	41788	W.	43	M.	iii	Post. wall	1 x 1½ cm.	Oval	"Firm,"	-	Normal
10	41981	C.	42	M.	i	Ant. wall	4½ x 3½ cm.	Oval	"Firm,"	Normal	Myomas of uterus (8½ x 9 x 8 cm.)
11	45943	W.	43	M.	i	Ant. wall	3 cm.	Oval	"Firm,"	Normal	Myomas of uterus (6½ x 6½ x 5 cm.)
12	48736	W.	39	M.	iii	Ant. wall	2½ cm.	Oval	"Tense,"	Normal	Myomas of uterus Normal



case reported by Cordaro,<sup>32</sup> a patient with a large myoma in the vagina suffered a rupture of the uterus during the course of a prolonged labor and died.

In other cases, including our Case 12, a small vaginal myoma was known to be present throughout the course of a pregnancy, no significant increase in the size of the tumor occurred, and no difficulty in labor was encountered.

#### DIFFERENTIAL DIAGNOSIS

As has already been indicated, myomas of the vagina may simulate malignant tumor but more often are mistaken for urethrocele, cystocele, prolapsus uteri, vaginal cyst, and even adenomyoma of the vaginal wall. Conversely, in a case recently observed by the authors (J.H.H., Gyn. Path. No. 48488), a nontender, firm, suburethral mass of four years' duration, was thought to have been a vaginal myoma, and only at operation was the condition correctly diagnosed as a chronic suburethral abscess.

Careful pelvic examination, including cystoscopic study, when the lesion to be diagnosed is in the anterior wall, will usually suffice for preoperative study. If the various possible conditions are kept in mind by the surgeon, the correct diagnosis will become apparent at operation.

#### TREATMENT

In 11 of our 12 cases, surgical excision was easily carried out and gave satisfactory results. In the remaining case of our series, treatment of the vaginal tumor did not seem indicated because of another disease which shortly caused the patient's death. Difficulties may be encountered because of unusual size of the tumor, or because of its intimate relationship with adjacent structures, particularly the urethra and bladder. Müller<sup>10</sup> has cited a case in which the bladder was entered during the surgical removal of a myoma of the anterior vaginal wall, and a vesicovaginal fistula resulted. In an occasional case irradiation may be the treatment of choice because of the poor general condition of the patient.<sup>25</sup>

#### PATHOLOGY

The vaginal mucosa is usually free from the underlying myoma, and this was true in the cases we studied. However, compression necrosis and ulceration of the mucosa may occur. The great majority of these myomas are encapsulated, but a case of diffuse myoma of the vaginal wall has been described by Downing.<sup>5</sup> In our cases microscopic examination showed the tumors to be composed of fibromuscular tissue with a predominance of the muscular elements. We observed no significant hyalinization or other degenerative changes, although the various types common to uterine myomas have been described.<sup>10, 27, 33</sup> Also, as in uterine myomas, it is possible that secondary sarcoma formation may occur, but no convincing evidence of this change can be found in the literature.

#### ETIOLOGY

It has been assumed by some authors that the origin of vaginal myomas is comparable with that of uterine myomas. While the exact etiologic factors in neither are known, statistics clearly show that the uterus, of all organs in the body, has a strong diathesis for myomatous tumor formation. Kelly and Cullen<sup>14</sup> in a thorough study of 1,674 cases of myomas of uterus found an associated myoma of the vagina in only a single case. In the same material they found one patient with a myoma of the Fallopian tube, and 3 patients with fibroid tumors of the ovary. In this study, it was apparent that the factors which caused the development of myomas in the uterus, did not exert any similar action on other Müllerian derivatives.

The negro race has a strong tendency to uterine myoma formation, but in relation to vaginal myoma this tendency not only fails to appear, but indeed seems to be reversed. In 9,000 consecutive autopsies performed in the Johns Hopkins Hospital, there were 1,560 women past 19 years of age, and of these, 719 were

posterior wall. Analyses of cases in which the necessary data were available have shown the distribution of sites of origin recorded in Table II.

TABLE II. DISTRIBUTION OF SITES OF ORIGIN OF VAGINAL MYOMAS

AUTHOR	NO. OF CASES	ANT. WALL PER CENT	POST. WALL PER CENT	RT. LAT. WALL PER CENT	LT. LAT. WALL PER CENT
Nürnberg <sup>26</sup>	90	67.8	21.1	6.7	4.4
Tonrneux <sup>1</sup>	120	55.0	25.8	10.0	9.2
Stein <sup>11</sup>	11	65.0	22.5	0.0	12.5
Bennett and Ehrlich	11	45.4	36.4	0.0	18.2

Regarding the distribution of myomas in the upper and lower halves of the vagina, Nürnberg<sup>26</sup> found an almost equal distribution between the two: of 33 cases analyzed, 12 arose in the upper half, 15 in the lower half, and in 6 cases both halves were involved.

*Consistency.*—Like myomas elsewhere, vaginal myomas are most often firm in consistency. In 11 of our patients, this was true. In the other patient (Case 12 in Table I), the myoma was rather soft and a diagnosis of urethrocele was made at the time of initial examination, but six years later, when the patient was re-examined, the mass had increased in size, was tense, and was thought to be a thin-walled cyst.

Downing's case<sup>5</sup> presented the typical physical findings of a cystocele, and it was only during operation that the true nature of the mass was discovered. Mattson<sup>6</sup> had a similar case in which the myoma arose in the anterior vaginal wall, was soft, and resembled a cystocele. Cystoscopic examination, however, revealed a "hillock" instead of a "depression" at the base of the bladder, and on the basis of this observation a diagnosis of tumor of the anterior vaginal wall was made. This was confirmed at operation when the myoma was removed. Ingraham<sup>27</sup> described a case in which the vaginal outlet was relaxed, and, when the patient strained down, a myoma, which arose in the anterior wall of the vagina, was forced from the outlet in such a way as to simulate a cystocele.

### SYMPTOMS

In cases of vaginal myoma, the development of symptoms depends on the size and location of the tumor and on the degenerative changes which may occur in the overlying mucosa as well as in the tumor itself.

*Urinary.*—In a considerable number of reported cases, and also in our Cases 4 and 7, the myoma lay near the urethra and, by pressure, gave rise to difficulty and frequency of urination. In one reported case,<sup>28</sup> complete urinary retention occurred and catheterization was necessary. In another case urinary incontinence developed.<sup>2</sup> In a most remarkable case described by Halban,<sup>29</sup> a large vaginal myoma caused obstruction of the urethra and intense dysuria with subsequent hematuria. Later pressure on one ureter resulted in hydronephrosis and hydroureter for which nephrectomy was performed before the vaginal condition was recognized.

*Protruding Mass.*—In our Cases 8 and 10, a protruding mass constituted the patient's chief complaint.

*Symptoms Secondary to Degenerative Changes.*—Ulceration of the adjacent mucosa did not occur in any of our cases. This complication has been described,<sup>3, 8, 10, 30</sup> however, with resulting purulent discharge and bleeding. In one case, severe hemorrhage occurred following ulceration.<sup>30</sup>

*Rectal Symptoms.*—According to Nürnberg, rectal symptoms are rare as a complication of vaginal myomas, but one such case has been reported.<sup>31</sup>

*Dyspareunia.*—Obviously when the tumors attain any considerable size, dyspareunia may occur.<sup>8</sup>

*Symptoms Associated With Pregnancy.*—In association with pregnancy, difficulty in labor has been encountered in cases with large vaginal myomas. In one unusual

(22) *Hofmöl*: Wien. med. Presse, p. 1229, 1891. (23) *Phillips, J.*: Brit. M. J. 1: 262, 1899. (24) *Cited by Nürnberger*: Veit-Stoeckel, Handbuch der Gynäkologie, ed. 3, Munich, 1930, J. F. Bergmann 5,2: p. 480. (25) *Tyler, A. F.*: Nebraska State M. J. 19: 257, 1934. (26) *Nürnberger*: Veit-Stoeckel, Handbuch der Gynäkologie ed. 3, Munich, 1930, J. F. Bergmann 5,2: p. 482. (27) *Ingraham, C. B.*: AM. J. OBST. & GYNEC. 14: 251, 1927. (28) *Smith, R. R.*: Am. J. Obst. & Dis. Women 45: 155, 1902. (29) *Halban*: Zentralbl. f. Gynäk. 1: 572, 1909. (30) *Byford, H. T.*: Am. J. Obst. & Dis. Women 18: 1104, 1885. (31) *Schestopal, M. W.*: Zentralbl. f. Gynäk. 1: 115, 1910. (32) *Cordaro, V.*: Ibid. 1: 762, 1905. (33) *Tuberowsky, D.*: Ibid. 50: 483, 1926.

## PERFORATION OF THE INTESTINE AFTER X-RAY AND RADIUM THERAPY OF CANCER OF THE CERVIX

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THIS report presents the details of a case in which intestinal perforation followed radiation therapy. The unusual method of metastasis as shown at autopsy is also of interest.

On May 22, 1936, Miss J. M., aged 40 years, was first seen complaining of slightly irregular menses. There was no bleeding between the periods at any time. Her past history was essentially negative except for one induced abortion, fifteen years before, at two months.

The general physical examination was negative except for hypertension (178/100). On pelvic examination the external genitals were negative; pelvic floor was excellent; fornices were shallow; cervix was unusually hard,  $3\frac{1}{2}$  cm. in diameter and smooth. The uterus was in second degree retroversion, normal in size and movable; adnexa were negative. No masses, tenderness or indurations were felt. A spot of blood was noticed on the examining finger at the end of the examination. A digital rectal examination was negative.

On June 12, 1936, a diagnostic curettage was done, at which time squamous cell carcinoma of the cervix was found.

Between June 18, 1936, and July 30, 1936, there were 32 deep x-ray treatments given, through 6 portals, 2 anterior, 2 posterior, and 2 lateral, 300 r. each at 50 cm.

On Aug. 15, 1936, 7,000 mg. hours of radium were given with 1 mm. platinum screen. Ten milligrams were placed in the fundus, 20 in the endocervix, 20 in the right fornix, and 20 in the left fornix. The radium capsules in the fornices were wrapped in 1 cm. of plain gauze.

Approximately one year later she began bleeding with each stool. Cramps were more severe and were relieved with paregoric and phenobarbital. She did not lose any weight and continued her work as a saleslady.

The following February the symptoms became more acute, although the bleeding was never profuse. A barium enema was given which showed an ulcerated area in the upper sigmoid.

On April 4, 1938, she was again admitted to the hospital complaining of pain in the left lower quadrant of four months' duration, with the diagnosis of extensive carcinoma plus pyometra. On April 16, 1938, a diagnostic curettage was done. A fine probe could just be inserted into the cervix. One tablespoon of thick, gray yellow, necrotic tissue was removed. Microscopic study showed carcinoma in advanced necrosis (Fig. 1).

Following this procedure she was temporarily relieved, but on May 16, 1938, she had an acute attack of abdominal pain, became cold and clammy and died in shock, two hours later.

colored and 841 white. The incidence of uterine myomas in the colored patients was 28.5 per cent and in the white patients, only 10.3 per cent. In this particular series not one case of vaginal myoma was observed. In the authors' 12 cases of vaginal myoma, 9 of the patients were white and only 3 colored, while the clinical material from which these cases came is more than half colored.

While myomas of the uterus are far more common than myomas in other parts of the body, myomas of the vagina occur even less frequently than myomas in the gastrointestinal tract. Here again the high race predominance in negroes is not found. In the 9,000 autopsy cases mentioned above, there were 8 cases of myomas of the gastrointestinal tract in women, 7 of whom were white.

#### SUMMARY

1. Twelve cases of primary myoma of the vagina are reported, and the literature is discussed.
2. The difficulties often encountered in diagnosis are cited.
3. The incidence of myomas of the vagina, the gastrointestinal tract, and the uterus is discussed, and its bearing on the question of etiology is considered.

#### CONCLUSIONS

On the basis of these figures we may conclude: (1) Myomas occur in the uterus far more frequently than elsewhere in the body, being present at autopsy in almost 20 per cent of all women past 19 years of age (2) Myomas of the uterus are almost three times as common in colored as in white women. (3) Myomas of the vagina occur not only far less frequently than myomas of the uterus, but even less frequently than myomas of the gastrointestinal tract. (4) Myomas of the vagina are probably less frequent in the colored than in the white. (5) The factors, whatever they may be, which so frequently induce myoma formation in the uterus, have no more effect on the production of myomas in the vagina than on the production of the same type of tumor in the gastrointestinal tract.

Theories ascribing the origin of vaginal myomas to Gärtner's duct or other embryologic remnants, seem untenable, since it is recognized that myomas develop in all parts of the vagina. The incidence of vaginal myomas is comparable not with that in the uterus but rather with that in extragenital smooth muscle viscera, such as the gastrointestinal tract.

#### REFERENCES

- (1) *Cited by Tournoux*: Progrès méd. 41: 1569, 1934. (2) *Gemmell, J. E.*: J. Obst. & Gynaec. Brit. Emp. 15: 286, 1909. (3) *Knauer*: Zentralbl. f. Gynäk. 1: 619, 1902. (4) *Simpson, G. F. B.*: Practitioner 76: 243, 1906. (5) *Downing, W.*: J. A. M. A. 98: 1157, 1932. (6) *Mattson, H.*: Ibid 103: 409, 1934. (7) *Kulikowska, L.*: Bull. Soc. d'obst. et de gynéc. de Paris 25: 335, 1936. (8) *Smith, R. R.*: Am. J. Obst. & Dis. Women 45: 145, 1902. (9) *Kleinwächter, L.*: Ztschr. f. Heilkunde 3: 335, 1882. (10) *Müller, R.*: Arch. f. Gynäk. 102: 511, 1914. (11) *Stein, A.*: Monatschr. f. Geburtsh. u. Gynäk. 78: 191, 1928. (12) *Nürnberg, L.*: Veit-Stoeckel, Handbuch der Gynäkologie, ed. 3, Munich, 1930, J. F. Bergmann 5,2: p. 473. (13) *Potel, G.*: Rev. de gynéc. et de Chir. Abdom. 7: 387, 1903. (14) *Kelley and Cullen*: Myomata of the Uterus, Philadelphia, 1909, W. B. Saunders Co., p. 204. (15) *Piccagnoni, G.*: Policlinico 28: 8, 1921. (16) *Martin, A.*: Ztschr. f. Geburtsh. u. Gynäk. 3: 406, 1878. (17) *Strachan, G. I.*: Proc. Royal Soc. Med., Section Obst. & Gynaec. 19: 78, 1926. (18) *Nürnberg, L.*: Veit-Stoeckel, Handbuch der Gynäkologie, ed. 3, Munich, 1930, J. F. Bergmann, 5,2: p. 489. (19) *Dicke*: Zentralbl. f. Gynäk. 1: 540, 1913. (20) *Pistuddi, A.*: Clin. ostet. 32: 396, 1930. (21) *Simon*: Zentralbl. f. Gynäk. 1: 306, 1908.

darkly-stained cells, which reveal a more or less cylindrical shape pointing out at the original glandular type of carcinoma (Fig. 4).

Most striking in the autopsy findings was the unusual spread of the carcinoma. The histolytic capacity of the tumor was apparently much greater than the tendency to give distant metastases. The small nodule which was found in the lung was the only evidence of distant metastatic extension of the tumor (evidently blood stream metastasis). There was no evidence of the involvement of lymphatic nodes any-



Fig. 2.

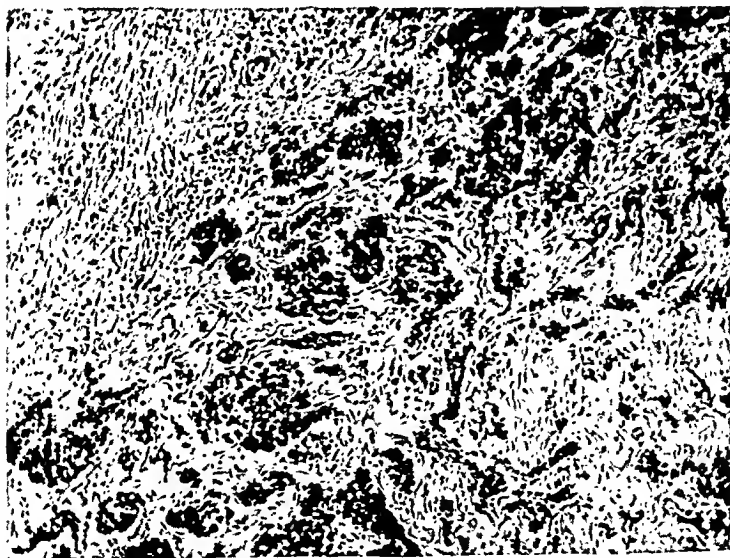


Fig. 3.

where in the abdominal or thoracic cavities. The carcinoma grew through the wall of the uterus extending from there in direct continuity into the omentum and the wall of the large bowel which were firmly adherent to the surface of the uterus. From the omentum, because of the adhesions between the latter and the anterior abdominal wall, the carcinoma involved the peritoneal covering of the abdominal wall and extended from there by direct continuity upon the abdominal surface of the diaphragm.

*Autopsy.*—(Dr. Leon Motyloff.) Record No. 66521, Path. No. 50300.

Following are the excerpts of the autopsy report with the essential post-mortem findings: The approach into the peritoneal cavity was difficult because of extensive adhesions between the omentum and anterior wall on one side and between omentum and pelvic organs on the other side. Greenish, purulent fluid with fecal odor filled out the spaces between the intestinal loops and the large pockets formed by the extensive adhesions.

The peritoneum of the anterior abdominal wall and the abdominal surface of the diaphragm were covered with densely seated multiple nodules reaching the size of a pea. The entire omentum was also infiltrated with the same kind of nodules. The lower portion of the omentum formed a large tumor mass of not less than 5 inches in diameter. This tumor mass was directly adherent to the uterus. The surface of the latter was entirely covered with densely seated carcinomatous nodules. The wall of the uterus was entirely destroyed by the carcinoma; it presented a mixture of tumor and scar tissue.

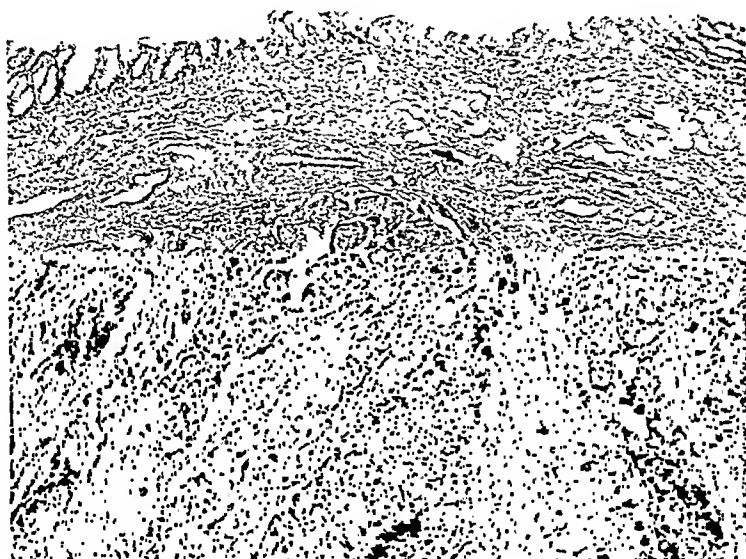


Fig. 1.

The sigmoid was adherent to the uterus and to the above-mentioned tumor of the omentum. An opening about 3 cm. in diameter with ragged edges was found in the sigmoid about 18 cm. above the anus. The perforated area of the intestine was intimately fused with the surface of the uterus. The portion of the bowel adjacent to the above-mentioned area of the perforation was infiltrated with the carcinoma. The perforated area was in free and direct communication with the above-mentioned large pockets filled with greenish fluid of fecal odor.

The soft parts of the pelvis were transformed into a necrotic tumor mass, in direct continuation with the carcinomatous nodules covering the surface of the uterus.

Following are the organs in which metastases were found: (1) Two small metastatic nodules at the lower surface and anterior edge of the lateral portion of the right lobe of the liver (superficial metastases). (2) A nodule 0.5 cm. in diameter at the apex of the left lung. The microscopic examination of the sigmoid at and in the vicinity of the perforated area revealed that the carcinoma invaded the entire wall of the intestine without actual penetration into the mucosa proper. However, the parts of the mucosal membrane which were overlying the carcinoma were entirely necrotic (Fig. 1).

The carcinoma presents everywhere a mixture of: (1) Large sheaths of flattened cells with marked hornification (Figs. 2 and 3). (2) Irregular cords of small

## SUCCESSFUL USE OF PROGESTERONE IN A CASE OF REPEATED SPONTANEOUS ABORTION

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C. G. D., a 36-year-old, Russian Jewish housewife, Bronx Hospital No. 109937, married twelve years, complained of inability to carry her pregnancies to term.

There was no familial history of hereditary illnesses, sterility, or habitual abortion. Both the patient and her husband have siblings married and with children. One of the patient's sisters has 12 children. The patient's past history was noncontributory, except for typhoid fever and pertussis and for the privations she suffered during and after the First World War in Europe. The menarche occurred at the age of sixteen; the periods lasted from one to two days and the flow was slight. Until her marriage, the patient experienced severe dysmenorrhea. Venereal diseases were denied by name, symptoms, and laboratory tests.

The patient was married in the United States in June, 1927. She and her husband were well-matched emotionally and intellectually and were anxious to have children. The patient's first spontaneous abortion occurred in August, 1927, after one missed menstrual period. In November of the same year there followed another spontaneous abortion at three months. It was suggested that "straightening the womb" would aid pregnancy; this was done without external scars in February, 1928. The operation was futile, however, as the patient again aborted spontaneously in August, 1928, at three months.

For the next few months the patient attended an outpatient department, where she says that many tests, including the Huhner and Rubin tests, were done, with normal results. By this time, the lack of a child in the family had become the source of much marital bickering and discussion as to which partner was at fault. In fact, there were a number of temporary separations.

The patient became pregnant again in the spring of 1929. She spent the next five months in bed, as near to complete rest as possible. In October she aborted twins. There was a septic postabortal course, for which a curettage was performed. She developed a severe urinary infection and was under treatment for the remainder of the year in another outpatient department.

An abortion in the second month occurred in October, 1931, following which a curettage was done. January, 1932, brought a two-and-one-half-month abortion. In September, 1932, after a long period of bed rest, the patient aborted six month twins. And finally in May, 1935, there was an abortion at three months.

The writers were consulted in June, 1939. At that time the emotional and psychologic marital disturbances were marked. The patient had been told by other physicians that persistence in attempts to bear children would be futile and even dangerous. The general physical examination was essentially negative. The patient was obese, weighing 160 pounds and measuring 60¾ inches in height. Her uterus was retroverted and the cervix small. In the absence of any serious pathologic conditions and because of the urgent desire for a child, the patient was told that she might become pregnant at any time and was advised to take wheat germ oil capsules and to rest in bed as much as possible. She had a scant period in July; early in September a Friedman test confirmed the diagnosis of pregnancy.

At the end of September, exactly three months after the last menstrual period, the patient called us in because of vaginal hemorrhage and intermittent backache. Vaginal examination was not performed. An initial dose of one international unit of progesterone was given immediately, followed by one-half unit dose twice weekly.

From the uterus the carcinoma extensively infiltrated (by direct continuity) the soft tissues of the pelvis.

The patient died of fecal peritonitis caused by perforation of the bowel.

#### DISCUSSION

It is thought that the concentration and proximity of the radium capsules in the vagina, without due regard to the law of inverse squares,<sup>2</sup> resulted in injury to the intestinal mucous membrane and with carcinomatous infiltration contributed to the perforation. The daily roentgen dose (300 r.) was perhaps high, in view of the findings of Corscaden, Kasabach and Lenz.<sup>2</sup>

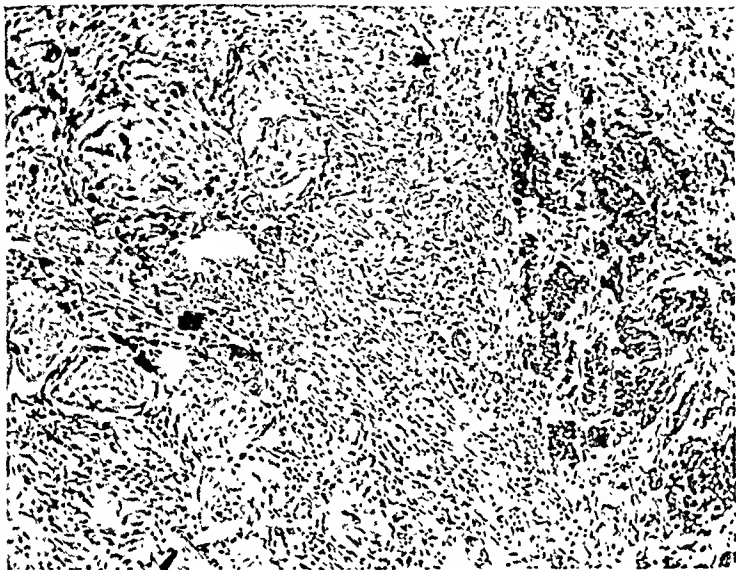


Fig. 4.

In 1935, Sackett<sup>3</sup> reported the complications following radiotherapy at Woman's Hospital, where smaller doses are usually given. These complications in the intestinal tract and also in the upper urinary tract were much less frequent in patients destined to survive five or ten years, than in those dying of carcinoma within five years. This suggests that the disease itself was more causative than the treatment. In his series there were no injuries like the one herein reported.

#### SUMMARY

1. A case report with autopsy findings following roentgen ray therapy for carcinoma of the cervix uteri is presented.
2. The importance of reducing the amount of radium in and about the cervix when the fornices are contracted is emphasized.

#### REFERENCES

- (1) Corscaden, J. A., Kasabach, H. H., and Lenz, Maurice: *Am. J. Roentgenol.* 39: 871, 1938. (2) Weyl, C., Warren, S. R., Jr., and O'Neill, D. B.: *Radiologic Physics*, Springfield and Baltimore, 1941, Charles C Thomas, p. 321. (3) Sackett, N. B.: *N. Y. State J. Med.* 35: 1, 1935.



## MORBIDITY FOLLOWING VAGINAL EXAMINATIONS DURING LABOR

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THE controversy over the relative merits of vaginal and rectal examinations during labor has apparently quieted down. Most teaching centers seem to have decided that rectal examinations are safer and; accordingly, many students are instilled with an abnormal fear of the vaginal canal which is unreasonable and acts as a barrier when "watchful expectancy" has outrun its usefulness.

In 1925 Mayes,<sup>1</sup> who employs vaginal examinations, instituted a technique of vaginal antisepsis with mercurochrome, and in 1929<sup>2</sup> reported a morbidity of 7.3 per cent in 8,900 cases. This or a similar technique has even been instituted as a method of "sterilizing" the operative field, in certain centers advocating rectal examinations. All varieties of "vaginal antisepsis" have come into favor, from simple instillations of antiseptic solutions with a syringe, to the elaborate compressed air machines for spreading the solution over the surface of the vagina. As a rule, the instillations are done at set intervals of time during labor and after examinations.

At the Millard Fillmore Hospital we do vaginal examinations almost exclusively. We do not employ vaginal instillations in most cases, agreeing with DeLee that it is not essential to successful obstetric practice. We cannot understand why, if rectal examinations are done for the purpose of avoiding possible contamination of the birth canal, one would deliberately invade that passage to spray some colored antiseptic fluid over its surface if the advantages derived from vaginal examinations are not obtained at the same time. We are not convinced that the repeated rubbing of the vaginal mucous membrane into the cervix from the rectum is safer than a vaginal examination, and we know that for purposes of identification of the dilatation and effacement of the cervix, presentation or prolapse of the cord, position of the fetus etc., vaginal examinations are definitely superior. All too frequently the belief that rectal examinations are without danger leads to far too many being done, and precaution against placing the thumb in the introitus is often neglected. Also the findings are frequently misleading, necessitating a vaginal examination for verification, or are definitely false. Many times we have seen a patient diagnosed by rectal examination as being ready for delivery, brought into the delivery room; put under an anesthetic, and then found to have a thin but practically undilated cervix. It is embarrassing to have to return such a patient to bed undelivered, but it is far wiser than to attempt delivery at this time, which is unfortunately sometimes done.

The vaginal bleeding quickly decreased and stopped altogether at the end of the week. The one-half unit dose was continued semiweekly for eighteen injections, after which one unit weekly was administered until the last month of pregnancy. At four-week intervals, corresponding to the time when the regular menstrual period would have come, an added injection was given in the middle of the week.

The patient continued to rest in bed. She took wheat germ oil capsules three times a day and occasional half grain phenobarbital and calcium lactate tablets, and observed a 1500 c.c. fluid salt-poor diet. Under this regime, gestation proceeded satisfactorily. The patient volunteered that she had never felt so well in her previous pregnancies as in this one. In other pregnancies she had suffered dysmenorrhea-like pain; now she felt quiet and perfectly relaxed. The blood pressure and urinalyses remained normal. The Wassermann test was negative. Fetal life was felt in November; the fetal heart was first heard in January, 1940.

Mild toxemia symptoms, slight edema and a faint trace of albumin, were noticed in March; restriction of fluids and salt was enforced. A troublesome hemangioma developed on the left thumb. Despite cauterization, it bled considerably, and irradiation was required in the post-partum period.

On April 8, 1940, the patient began to pass large amounts of amniotic fluid. She was admitted to the Bronx Hospital, and the drainage ceased after five days. She spent the last month of pregnancy in bed at the hospital; during this time no endocrine preparations were given.

The membranes ruptured and labor started spontaneously on May 7. Roentgenograms revealed the pelvis to be ample and the baby of normal size. Little progress, however, was noted. The cervix was thick and hard and did not dilate beyond two fingers. The head, which was in the left occiput posterior position, did not engage. Because of these indications, a low cervical cesarean section was performed on May 8, after a trial labor of twenty-four hours; a normal 6 pound 8 ounce girl was delivered. The mother's blood count on the day of delivery was: red blood cells 3.90 M., hemoglobin 9.6 Gm., or 66 per cent (Sahli), white blood cells 12,800; differential: polymorphonuclears 89 per cent, stab cells 1 per cent, lymphocytes 7 per cent, monocytes 3 per cent. The postoperative course was uneventful. On the day of discharge, May 22, fourteen days after birth, the baby weighed 6 pounds 14 ounces.

Within the reappearance of menstruation four months post partum, a bizarre sequel of the hormone injections manifested itself. The arms and buttocks, the sites of injection, became swollen, painful, tender, and hemorrhagic for the duration of the menstrual period. Up to the present writing, this has recurred four times.

The reaction at the sites of injection of the hormone, coincident with the menses, is probably a sensitization phenomenon. In our study of reported cases, we have found no mention of such a sequel to progesterone therapy.

51 EAST 90TH STREET  
981 FOX STREET

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Guggisberg, H.: Significance and Prevention of Congenital Struma, Arch. f. Gynäk. 167: 622, 1938.

The pathology of congenital struma is described at length and its relationship to maternal hypothyroidism and endemic goiter is discussed. In 1925, 53 per cent of babies born at the Bern Frauenklinik showed evidences of struma. The administration of iodine to the pregnant women throughout pregnancy during 1937 resulted in a reduction to 30 per cent. This reduction in congenital goiter depends solely upon iodine administration and is not related to maternal health. The author believes that endemic goiter could finally be eradicated and cretinism reduced to a minimum if iodine administration is continued not only throughout intrauterine life but also during childhood and maturity in order that a second generation may thus be produced under iodine therapy.

RALPH A. REIS.

TABLE I. GROSS MORBIDITY IN PERCENTAGE

	PER CENT OF CASES	AFEBRILE 98.6°-99° F.	FIRST FEBRILE 99.2°-100.2° F.	SECOND FEBRILE 100.4° F.
All cases	100.0	72.9	22.6	4.5
Private cases	95.4	73.0	22.5	4.5
Service cases	4.6	71.7	23.9	4.4
Deliveries per vaginam	93.9	75.6	21.6	2.8

TABLE II. MORBIDITY PERCENTAGE ACCORDING TO METHOD OF DELIVERY

METHOD OF DELIVERY	PER CENT OF CASES	AFEBRILE 98.6°-99° F.	FIRST FEBRILE 99.2°-100.2° F.	SECOND FEBRILE 100.4° F.
Spontaneous	25.0	82.0	17.2	0.8
Version and extraction	12.4	74.2	23.4	2.4
Breech extraction	4.0	82.5	15.0	2.5
Low forceps	48.2	73.5	23.2	3.3
Midforceps	4.2	61.9	31.0	7.1
High forceps	0.1	—	—	100.0
Cesarean sections	6.1	31.1	37.8	31.1
High classical	4.6	32.6	32.6	34.8
Low classical	0.5	80.0	—	20.0
Cervical	0.7	42.9	42.9	14.2
Porro	0.3	33.3	33.3	33.3

Table III shows the morbidity in terms of the kind of examination done, and also when vaginal instillations were employed. As stated above, there are too few of other than vaginal examinations for a just comparison.

TABLE III. MORBIDITY PERCENTAGE FOR METHODS OF EXAMINATION

	PER CENT OF CASES	AFEBRILE 98.6°-99° F.	FIRST FEBRILE 99.2°-100.2° F.	SECOND FEBRILE 100.4° F.
Vaginal examinations only	87.8	73.6	21.9	4.5
Rectal examinations only	2.5	72.0	24.0	4.0
Both vaginal and rectal examinations	2.7	81.5	18.5	—
Vaginal instillations employed	7.0	64.3	30.0	5.7

The average number of vaginal examinations per patient was 1.4. This is a very conservative estimate, for unfortunately many examinations are done which are not recorded on the chart, and some doctors examine their patients in the office before sending them to the hospital. We have not been able to demonstrate any direct correlation between the number of examinations done and the morbidity. However, when cesarean sections are excluded, it is seen by the figures in parentheses that the morbidity following none, one, and two vaginal examinations is about the same, and then the morbidity rate begins to rise, especially with an increase in the number of examinations above five.

Most patients remain ten to twelve days in the hospital following delivery, whether by normal or cesarean route. Only 16 of the 1,000 patients in this series remained fourteen days or longer post partum. Half of these were afebrile. Of the 4 remaining seventeen days or more, one had pyelitis, one was operated upon on the eighth day post partum for an ovarian cyst, with a resulting morbidity for two days, one was an afebrile cardiac, and the last had a third degree laceration and was in the first febrile zone for four days only.

## TECHNIQUE

Our routine on the maternity floor of the Millard Fillmore Hospital, a general hospital of 261 beds, where in 1940 there were 1,844 deliveries with 155 different operators, is the following: When the labor patient is admitted, she is immediately put to bed and the vulva is shaved, using only enough green soap and water to form a lather, thus minimizing the possibility of infected material entering the vagina. This is our only preparation before the patient is taken to the delivery room. When a vaginal examination is to be done, the obstetrician puts on a sterile glove, separates the labia with the fingers of the other hand, and then, using liquid green soap as a lubricant, gently inserts two fingers and makes his diagnosis. A sterile pad is then put over the vulva. When the patient is ready, she is taken to the delivery room where a nurse gently scrubs the vulva and surrounding area with green soap followed by sterile water, six perineal pads being used for this purpose. A sponge is then put over the rectum, the physician catheterizes the patient and, using green soap freely as a lubricant, confirms the position and proceeds with the delivery. We consider the free use of liquid green soap by the operator as very important. We have had no known aspirational green soap pneumonias, although Titus warns of this possibility.

However, the proof of the effectiveness of any method is in the results. When we talk about rectal or vaginal examinations during labor being "safer," we mean that they are followed by lower maternal mortality and less morbidity. In accord with Ziegler's<sup>3</sup> classification of morbidity, we have separated our cases into three groups:

Afebrile: No temperature over 99° F.

Zone 1: 99.2° to 100.2° F. in any two consecutive twenty-four-hour periods, excluding the first twenty-four hours following delivery.

Zone 2: 100.4° F. and over in any two consecutive twenty-four-hour periods, excluding the first twenty-four hours following delivery.

Temperatures are taken every four hours for the first five days following delivery per vaginam, for the first seven days following section, and then twice a day thereafter, unless there is an elevation.

## RESULTS

For the purpose of this study the last 1,000 consecutive deliveries were analyzed, beginning Sept. 3, 1940, and ending March 13, 1941. Since this period takes in late summer, fall, and winter, and a period during which there was a mild influenza epidemic in Buffalo, we consider it a fair criterion of our methods. Only patients five and one-half months pregnant or over are accepted on the maternity floor. Of course, with so many operators, there are a few who employ vaginal instillations and an occasional operator who does rectal examinations. Their results, though listed separately in the tables, are too few in number to justify comparison.

In this series of 1,000 consecutive cases there was no maternal death. The gross fetal mortality was 4.7 per cent and the corrected mortality 2.7 per cent. Service cases accounted for 4.6 per cent of the series.

In Table I is shown the gross morbidity, which was 4.5 per cent in the second febrile zone. It is significant that 19 of these 45 febrile cases were cesarean sections, so that the gross morbidity for deliveries per vaginam was only 2.8 per cent.

In Table II the series is analyzed according to the various methods of delivery, with their respective morbidities. Multiple pregnancies, of which there were 9, have been classified as the most difficult procedure employed for the delivery of either infant. Only 25 per cent of the cases were spontaneous deliveries. It is significant that the morbidity increases with the degree of operative interference, except in the case of versions which are performed almost entirely by a selected group of operators.

## PROLAPSE OF THE PLACENTA

### REPORT OF TWO CASES WITH DELIVERY OF LIVE BABIES

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PROLAPSE of the placenta is an infrequent complication of labor that rarely is reported. In the past twenty years, it has been presented in the medical literature only eight times. The last report in the English language was published by Rucker<sup>1</sup> in 1926. The incidence of this complication has been variously reported by different authors. It is reported to range from one case in 7,000 (Münchmayer<sup>2</sup>) to one case in 45,999 (Genter<sup>3</sup>). Sir James Y. Simpson,<sup>4</sup> in his memoirs, collected 141 cases, 56 being on record and the remainder from notes furnished by colleagues. Genter<sup>3</sup> reported 29 cases from the literature during the period of 1852 and 1913. Burczak<sup>5</sup> in the latest and most complete discussion of this complication gathered 46 cases from the literature and drew certain conclusions from their analysis. We have observed the following two cases during the past three years.

CASE 1.—M. D., white, aged 36 years, gravida viii, para vii, was admitted to the Michael Reese Hospital Prenatal Clinic on April 12, 1937. Her last menstrual period was July 20, 1936 and she was expected to be due on April 27, 1937. Her pelvis was considered to be adequate, and her blood pressure was normal. The position of the baby was R.O.T. and the fetal head was floating. She was seen one week later at the clinic without any abnormal findings. On April 27, 1937, at 2:10 A.M., she was admitted to the hospital (service of Dr. Julius E. Lackner) in good condition. Her pains were weak and she had a slight "bloody show." This "show" soon became more prominent and at 8:40 A.M., the bleeding was bright red and large in amount according to the nurse's record. Her condition was very good. The blood count was 3,750,000 red count and 70-80 per cent hemoglobin (Tallqvist). At 10:30 A.M., a vaginal examination was performed with all preparedness available to cope with any bleeding that might ensue from the manipulation. A placenta previa lateralis over the posterior cervical lip was felt. Bleeding followed this examination and an 8 cm. intraovular bag was immediately inserted. A one-pound traction weight was added. The patient's condition was still very good. Donors were called and three were found compatible. At 1:01 P.M., or two and one-half hours after its insertion, the bag was expelled spontaneously. It was followed by a moderate amount of bright red vaginal bleeding. The patient was set up immediately and a vaginal examination showed the cervix to be 7 cm. dilated. A Braxton Hicks' version was begun at 1:25 P.M. (by A. J. K.) and the foot was brought down in two minutes. The placenta was expelled spontaneously as the foot was brought out. The baby was permitted to come through the cervix with gentle traction and with no intention to do an immediate extraction. When the head was button-holed by the cervix there was no further traction applied to the baby. The latter was not expected to survive. The face had passed the cervix which was firmly around the crown of the head. The perineum was retracted by the hand to allow air to reach the baby's mouth. The head gradually passed the cervix, aided by pressure of the assistant's hand above the symphysis. The baby, moderately asphyxiated, weighing 3,250 Gm. (7 pounds 2½ ounces), was born nine minutes after the delivery of the placenta. The uterus was immediately packed tightly. Ten minutes later the patient went into profound shock. She was given a transfusion without any delay because the donors had been kept available in the corridor outside the delivery room. She was given 550 c.c. of whole blood and 1,000 c.c. of 5 per cent glucose. The red

TABLE IV. RELATION OF NUMBER OF EXAMINATIONS TO MORBIDITY

NUMBER OF VAGINAL EXAMINA- TIONS	NUMBER OF CASES	% AFEBRILE 98.6°-99° F.	% 1ST FEBRILE 99.2°-100.2° F.	% 2ND FEBRILE 100.4° F.
0	283 (239)*	70.0 (77.0)*	22.6 (20.1)*	7.4 (2.9)*
1	341 (337)*	75.4 (76.2)*	21.7 (21.4)*	2.9 (2.4)*
2	190 (187)*	77.9 (78.1)*	19.5 (19.8)*	2.6 (2.1)*
3-5	150 (146)*	49.3 (49.4)*	46.7 (46.5)*	4.0 (4.1)*
Over 5	11 (9)*	63.6 (66.7)*	18.2 (22.2)*	18.2 (11.1)*

\*Excluding cesarean sections.

### SUMMARY

We are reporting a series of 1,000 consecutive cases delivered on the maternity floor of a general hospital. There were no maternal deaths and the corrected fetal mortality rate was 2.7 per cent. Seventy-five per cent of the deliveries were operative. Vaginal examinations alone or vaginal and rectal examinations were done in 97.5 per cent of the cases. Vaginal instillations were employed in 7 per cent. The gross morbidity for all deliveries was 4.5 per cent for the second febrile zone, and 22.6 per cent for the first febrile zone. Excluding sections, the respective morbidities were 2.8 per cent and 21.6 per cent. Following delivery, 1.6 per cent of the patients remained fourteen days or over in the hospital and half of these were afebrile.

### CONCLUSIONS

1. Vaginal examinations during labor, when done carefully and not too often, are safe, and we believe the procedure of choice.
2. Vaginal instillations at intervals during labor and following examinations are not essential to safe obstetrics and impress us as tending toward "meddlesome interference."

### REFERENCES

- (1) *Mayes, H. W.*: AM. J. OBST. & GYN. 10: 61, 1925. (2) *Idem*: Ibid. 17: 645, 1929. (3) *Ziegler, C. E., and Austin, B. R.*: Pennsylvania M. J. 43: 1452, 1940.

Bleyer, A.: Rôle of Advancing Maternal Age in Causing Achondroplasia, Am. J. Dis. Child. 58: 994, 1939.

In an attempt to determine the effect of maternal age as cause of achondroplasia, Bleyer found only 47 cases in a review of the literature in which the age was mentioned or could be obtained from the author. Sending letters to heads of pediatric and orthopedic departments of many schools and hospitals in this country and Canada, he obtained data on 256 additional cases. As with mongolism, the influence of maternal age in cases of achondroplasia appears to start at or soon after the beginning of the reproductive period and increases steadily to its end. Therefore, it seems that the risk of bearing a child with either of these anomalies increases, if only by a little, with the passing of each menstruation. "Advancing" rather than "advanced" maternal age is the term to be preferred in designating this factor. Whether in these situations maternal age is in itself a cause of the defects or whether it is coincidental with another factor, as yet undetermined, is of course unknown.

J. P. GREENHILL.

The pathogenesis of this accident of labor depends upon the site of implantation of the placenta and upon the existence of one or more of various mechanical factors. When the placenta is placed over or near the dilating cervical os, it is logical that detachment may occur as the cervix dilates. If the head remains high, prolapse of the placenta is more likely. When, however, the site of nidation is higher in the uterine segment or the placenta is normally implanted, some other factor or combination of factors must come into play. deVink<sup>9</sup> postulates that there is a deficiency of the trophoblast and the decidua which allows for beginning separation. This author also considers other possible factors may be endometritis of the decidua with degeneration of the placental site, toxemias of pregnancy with infarctions of the placenta and possibly some hormonal upset. Other things which have been considered are heart disease, tuberculosis, syphilis, and severe nutritional diseases. At any rate toward the end of pregnancy, something happens which causes a tear in the spongy layer of the decidua. After this happens, some traumatic or mechanical factor takes place to complete the picture. This factor is usually something that will cause a change of the intrauterine pressure or uterine volume so as to allow separation of the contracting uterus from the noncontracting placenta. Such things may be: delivery of the first baby in multiple pregnancies (Barrelet<sup>10</sup> and Case 2 reported herein), sudden rupture of the membranes in hydramnios short umbilical cord, trauma to the abdomen, or intrauterine manipulation. A final factor which allows prolapse to occur is failure of a presenting part to adapt itself to the cervix so that the os is not blocked. Thus transverse presentation, a narrow pelvis with a high riding fetal head or certain monstrosities favor such a phenomenon (Larisch<sup>11</sup> and Miklós<sup>12</sup>).

Surprisingly, the clinical picture is much less acute than in *abruptio placentae*. Unless prolapse of the placenta occurs as a complication of placenta previa, bleeding during pregnancy is rare. Usually the patient is a multipara and has a normal course during pregnancy. The placenta loosens during labor without notice. The bleeding is frequently minimal or it may be entirely absent. Occasionally some severe bleeding may occur, and rarely does collapse ensue. In 40 of the cases reported by Bureczak,<sup>5</sup> 12 patients had no bleeding, 15 had slight bleeding, and in only 13 was the bleeding severe after rupture of the membranes. Simpson<sup>4</sup> emphasized the fact that hemorrhage ceased when the placenta was entirely detached and even advocated the artificial extraction of the placenta in certain cases of placenta previa. This lack of bleeding has been explained by deVink<sup>9</sup> as due to deficiency of formation of decidua. When some mechanical factor ensues causing easy separation of the placenta, the bleeding is minimal because the spongiosa is degenerated and its blood vessels are closed. The uterus contracting after separation of the placenta also aids in effectively controlling the hemorrhage. Later, there may be danger of uterine atony with associated hemorrhage. The location of the placenta is sometimes difficult to determine. In order to decide whether the placenta was originally in a normal location, Larisch postulated the following rules: (1) no placenta felt on vaginal examination, (2) no bleeding before labor was well advanced, (3) free blood above the child, (4) the opening in the membranes some distance from the placenta, and (5) no trauma to the placenta. These requisites are complied with in our Case 2 reported herein.

The prognosis for the child is bad. In Bureczak's<sup>5</sup> 46 cases, there were only 5 live births. Delivery must follow very soon after prolapse of the placenta. This, of course, depends on the promptness of action of the operator and on the dilatation of the cervix. If at the time of the unexpected occurrence of this accident, both the mother and the accoucheur are prepared for an immediate delivery, a live child is more likely to be obtained. This fortunate coincidence accounts for the delivery of live babies in our cases. The danger to the mother lies in atony of the uterus with hemorrhage when the placenta is separated or expelled. Considering the general mortality of certain of the etiologic factors, such as placenta previa, or *ablatio placentae*, that of prolapse of the placenta is not high. Various mortality reports of prolapse range from 1 death out of 15 to 10 out of 46 (Bureczak<sup>5</sup>). There is also danger of infection along the umbilical cord to the placental site.

count at this time was 1,800,000 and the hemoglobin 50-60 per cent. Two days later a second transfusion was given to the patient and she gradually improved. Both mother and baby left the hospital thirteen days later.

CASE 2.—W. H., a 23-year-old colored female, para iii, gravida iv, had her last menstrual period on Dec. 24, 1938, and she was calculated to be at term on Oct. 1, 1939. Her previous pregnancies had terminated uneventfully with a normal puerperium each time. Her children weighed from 5½ to 7 pounds at birth. Her prenatal course was normal although she did not present herself at the clinic until the seventh month. Her blood pressure and urine were normal, the Kahn test was negative, and the vaginal smear showed no gonococci. There was no history of bleeding at any time.

On Aug. 25, 1939, at 1:50 A.M., she was admitted to the Obstetrical Ward of the Cook County Hospital (Service of Dr. Daro), having been in active labor for one hour and fifty minutes. The cervix was completely dilated on admission to the ward; the membranes were intact; the station of the head was plus two and the fetal heart tones were 132. The abdomen appeared large for the stage of gestation. She was immediately prepared and draped for delivery.

Five minutes after admission, the membranes ruptured spontaneously, the fetal head followed and was delivered within the next few pains. The delivery was complete at 2:00 A.M. The cord was cut and clamped. The mass remained in the abdomen with its ovoid in the transverse. Fetal heart tones were noted, thereby establishing a diagnosis of twins. A vaginal examination was made by one of us (P. J. S.) to determine position and presentation but only a rapidly prolapsing bag of waters was felt. This followed the hand out of the vagina and ruptured spontaneously at 2:11 A.M. The hand was reinserted only to find a soft rapidly prolapsing mass of tissue. As the examiner's hand was again withdrawn a mass fell out of the vagina which proved to be the fused double placenta. The second cord was double clamped and cut. Internal examination revealed the position to be left scapula anterior. The operator grasped the lower foot and completed a version and extraction with moderate ease. Blood clots approximating 50 c.c. were expelled immediately after the baby. The latter was easily revived with a tracheal catheter and warm baths. The first twin was a male infant weighing four pounds five ounces; the second was a female weighing four pounds two ounces. Aside from small hard old white infarcts up to 2 mm. in diameter on the maternal surface, the placenta was normal. The shortest distance from the edge of the placenta to the site of rupture of the membranes was 15 cm. A double amnion and chorion were present.

#### DISCUSSION

This condition virtually represents a reversal in the order of the second and third stages of labor, the placenta being expelled before the fetus. The exact etiology of this condition is unknown. It almost always occurs in multipara. It frequently occurs in premature labors. Burezak<sup>5</sup> in 46 cases found the following relationship to term deliveries; 16 were full term, 10 occurred in the ninth lunar month, 12 were earlier than this, while in eight instances the period of uterogestation was not determined. The same author states that the etiologic factors of prolapse of the placenta are the same as those for *ablatio placentae*. Thus it may be related to the toxemias of pregnancy and hypertensive vascular disease. This was evident in the case report of Mulder<sup>6</sup> whose patient was nephritic with high blood pressure, and she also had a narrow pelvis and a highly placed fetal head. She developed an *ablatio placentae* with later prolapse of the placenta. This combination is also related to placenta previa which was present in Case 1 of our series, and was reported also by Nadler.<sup>7</sup> Münchmayer,<sup>8</sup> however, states that placenta previa should not be listed among the causes of prolapse of the placenta, because, she maintains, there must be a normal implantation to start with. Rueker<sup>1</sup> and deVink<sup>9</sup> disagree with this. Multiple pregnancy, transverse presentation, hydramnios, and narrow pelvis are also very important etiologic factors. Prolapse also occurs during attempts at version, especially with an associated placenta previa. (Nadler and our Case 1.)



pregnant woman. These were mild affairs. . . . It has been a constant surprise to us to see evidence of activity fail to appear.<sup>6''</sup>

As the reports of similar experiences are so few, it seems desirable to report the following case.

### CASE REPORT

E. D., a white, American, 29-year-old, married, para 0, gravida i, was admitted to Kings County Hospital on the service of Dr. Charles A. Gordon on May 7, 1940 from the cardiac obstetric clinic. The patient suffered from an original attack of rheumatic fever at the age of 4 years, with one recurrence at the age of 14. Acute osteomyelitis of the left leg occurred at 22 years of age but left no sequelae. The ante-partum course had been uneventful except for a brief episode of acute bronchitis for which she had been hospitalized and which cleared rapidly on bed rest alone. Admission had been advised as all cardiac patients are routinely hospitalized for rest at least two weeks prior to their expected date of confinement. The last menstrual period was Aug. 23, 1939, and the calculated date of confinement May 30, 1940.

Physical examination of the patient on admission revealed a young, well-developed woman who did not appear ill. The temperature was 99.2° F., the pulse 108, the respirations 24, and the blood pressure 124/94. Regular sinus rhythm was present. The heart was enlarged beyond the mid-clavicular line, the apex impulse being in the sixth interspace. Presystolic and systolic murmurs were heard at the apex. The second sound at the pulmonic area was accentuated. The lungs were clear. Obstetric examination revealed a normal pregnancy at term. She was not in labor. *Laboratory data:* The urine was negative. The blood count was 3.4 million red cells, 7,200 leucocytes with 76 per cent polymorphonuclear leucocytes and 64 per cent hemoglobin.

On the day following admission, the temperature, pulse and respiratory rate returned to normal and remained so until May 12 (six days after admission), during which time she had no symptoms. On this date, the temperature began to rise, reaching 99.2° F., accompanied by an increase in the pulse rate to 90. This continued the following day and was associated with a mild gastrointestinal upset, manifested by nausea, vomiting, and anorexia. At this time, the urine contained acetone but no diacetic acid. Vomiting ceased twenty-four hours later and the acetone disappeared from the urine. The status remained unchanged until May 15, when for the first time, she complained of pain in the left sacroiliac, shoulder and elbow joints. No redness or swelling was apparent, but these articulations were tender to palpation. The temperature at this time ranged between 100.6° and 101.8° F. with a pulse rate of 96 to 106. The blood count was 4.37 million red blood cells, 12,300 white blood cells with 79 per cent polymorphonuclear leucocytes and the hemoglobin 67 per cent. The sedimentation rate was 24 mm. in thirty-five minutes. An electrocardiogram revealed sinus tachycardia. Sodium salicylate with sodium bicarbonate was administered in doses of gr. xx three times daily but failed to alleviate the symptoms or to affect the temperature and pulse rate. The dosage was, therefore, increased to gr. xxx, t.i.d., also without effect, while further increase in dosage caused salicylism. On May 17, a musical, systolic, gruntlike murmur was heard at the fourth interspace, just to the left of the sternum. Next day, the pain in the joints had decreased considerably but the left wrist became involved and was excruciatingly painful. At this time the blood count was 3.12 million red cells, 10,000 white cells with 80 per cent polymorphonuclear leucocytes and the hemoglobin 64 per cent. An electrocardiogram showed only sinus tachycardia. The temperature on this day declined to 98.8° F. but the pulse rate remained at its previous level. Within the next twelve hours, the original joint manifestations gradually but completely disappeared.

At 3:15 A.M. on May 19, labor started and a six-pound two-ounce, living female infant was delivered at 7:45 A.M. by prophylactic outlet forceps under novocaine anesthesia. Following delivery the temperature ranged between 99° and 101° F. for six days, returning to normal on May 25 and remained unchanged until discharge. During this period, the pulse ranged between 90 and 124. Salicylates were continued in doses of gr. xx four times daily until May 28. Repeated sedimentation rates during this interval consistently showed a fall of 24 mm. in fifteen to twenty

## SUMMARY

1. Two cases of prolapse of the placenta with delivery of live babies are presented and the literature is discussed.

2. This complication most frequently occurs in multiparae and in premature labors. It is associated with placenta previa, ablatio placentae and toxemias of pregnancy.

3. Prolapse of the placenta is favored by the following factors: The first, initiating separation; then, some mechanical factor causing a sudden change in intrauterine pressure, and last, an uncovered cervical os permitting free extrusion of the placenta. Clinical examples of these factors were enumerated.

4. The symptomatology is frequently benign. Hemorrhage, fortunately, is not marked. In typical cases, the placenta has a normal implantation. However, placenta previa may be complicated by this phenomenon.

5. The prognosis for the infant is extremely unfavorable, while for the mother, the outlook is surprisingly better.

6. If feasible, immediate delivery from below, usually by version and extraction, is the treatment of choice.

## REFERENCES

- (1) *Rucker, M. P.*: AM. J. OBST. & GYNEC. 11: 189, 1926. (2) *Münchmayer*: Quoted by Miklós. (3) *Genter*: Quoted by deVink. (4) *Simpson, J. F.*: Month. J. Med. Sc. 158: 169, 1845, quoted by Rucker. (5) *Burczak, N.*: Zentralbl. f. Gynäk. 58: 1829, 1932. (6) *Mulder, W. J.*: Nederl. tijdschr. v. geneesk. 2: 5871, 1929. (7) *Nadler, J.*: Schweiz. Med. Wehnschr. 51: 854, 1921. (8) *Münchmayer, F.*: Quoted by Rucker. (9) *deVink, L. P. H. J.*: Nederl. tijdschr. v. geneesk. 82: 2985, 1938. (10) *Barrelet*: Schweiz. med. Wehnschr. 60: 828, 1930. (11) *Larisch*: Monatschr. f. Geburtsh. u. Gynäk. 67: 278, 1924. (12) *Miklós, L.*: Orvosi Hetil. 79: 646, 1935.

185 NORTH WABASH AVENUE

## ACUTE RHEUMATIC FEVER COMPLICATING ADVANCED PREGNANCY

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**A**CUTE rheumatic fever complicating advanced pregnancy is of such rare occurrence as to warrant individual case reports.

Bramwell and Longson,<sup>1</sup> in a review of their experience with 350 obstetric cardiacs, state, "We have not yet met with any case of acute articular rheumatism or of acute rheumatic carditis during pregnancy." Similar observations have been made by MacKenzie<sup>2</sup> and by Jensen.<sup>3</sup>

Schaeffer,<sup>4</sup> in 1886, reported a case of a 35-year-old gravida who developed acute rheumatic polyarthritis four days before the onset of labor. She was treated with salicylates and immobilization, and was delivered normally of an apparently healthy baby. Heffernan<sup>5</sup> described a 25-year-old primipara who, during the eighth month of pregnancy, developed acute rheumatic fever. Despite the liberal use of salicylates, the condition grew worse and after three weeks of conservative treatment, labor was induced and delivery effected. "The remarkable feature of the case was the rapid response to antirheumatic treatment when the uterus was emptied."<sup>5</sup> Hamilton, summing his experience of 850 cardiac obstetric patients, states that "in only seven instances have we been tempted to diagnose active rheumatic disease in a

# LITHOPEDITION ASSOCIATED WITH NORMAL TERM PREGNANCY AND SUBSEQUENT RUPTURED TUBAL PREGNANCY

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THIS case is reported, not only because of its rarity, but also because of its clinical interest.

C. L., a British West Indian colored female, aged 30 years, was brought by ambulance to the Sydenham Hospital on July 12, 1940. She complained of severe abdominal pain and vaginal bleeding.

On Jan. 26, 1940, five and one-half months before, the patient had given birth to a full-term, normal baby. The labor was unattended, and the post-partum course was uneventful. One month after delivery, she resumed coitus.

On May 19, 1940, four months after delivery, she experienced vaginal bleeding, which she interpreted as her first post-partum period. In June, 1940, there was scant bleeding, with clots, of two days' duration. On July 9, 1940, three days before her admission to the hospital, intermittent spotting of blood occurred. On July 11, twenty-seven hours before admission, the patient had a sudden non-radiating, lancinating pain in the right lower quadrant. This was followed by progressive abdominal enlargement. There was no fainting.

Examination following admission to the hospital revealed a well-developed, well-nourished negress, 30 years of age, who appeared acutely ill. The pulse was regular, of fair quality, with a rate of 112; the systolic blood pressure was 130 and the diastolic 92. The temperature was 99.6° F.; the respirations 24. She was apprehensive. The conjunctivas and nail beds showed marked pallor. The tongue was dry and furred.

The abdomen was distended, tender throughout, and rigid. There was marked rebound tenderness. Shifting dullness was elicited.

Gynecologic examination showed a parous introitus. The cervix was soft, not patulous, and tender on motion in all directions. The uterus could not definitely be mapped out because of the distention and rigidity. A tender mass bulged into the left half of the posterior fornix.

Blood examination showed 54 per cent hemoglobin, a white count of 12,600, and a sedimentation rate of 14. Wassermann and Kahn tests were negative. Urinalysis showed faint traces of albumin and sugar; urobilinogen was 2-plus; there were hyaline casts and a few white and red blood cells.

A diagnosis of left ruptured ectopic pregnancy was made, and the patient was prepared for immediate operation.

Upon opening the abdomen, a large quantity of blood, with fresh and old clots, was found. There was a large, hard mass wrapped in omentum and loosely adherent to the cecum. This had the appearance of a calcified parasitic fibroid. When the omentum was freed, it became evident that we were dealing with a large lithopedion. The right ovary was enlarged by the presence of a corpus luteum of pregnancy, 3 cm. in diameter. The right tube was congested, but otherwise apparently normal. The uterus was the size of a six weeks' gravidity, soft and blue. The left tube was represented by a fist-sized sac, through the posterior inferior angle of which there projected a 12 cm. sized fetus. The head was still contained within the sac. There was no evidence of a placenta in the abdominal cavity.

A left salpingo-oophorectomy was performed, the lithopedion dissected from its envelop, and the abdomen closed. The postoperative course was uneventful.

minutes, but on June 1, it increased to 180 minutes. The involvement of the left wrist disappeared within forty-eight hours of delivery. The murmur heard on May 17 likewise disappeared within three days after parturition. On June 1, the urine was negative, and the blood count was 3.26 million red cells, 11,100 white cells with 66 per cent polymorphonuclear leucocytes and the hemoglobin 78 per cent. Repeated blood cultures showed no growth. Thereafter the post-partum course was entirely uneventful, and she was discharged on June 13, twenty-five days post partum.

Since discharge she has been attending the cardiac clinic regularly and has experienced no diminution of cardiac reserve. The physical findings were similar to those reported on the first visit to the cardiac clinic.

Both immediately post partum and during its entire hospital stay, the baby showed no evidence of rheumatic fever or rheumatic carditis.

### DISCUSSION

The reason advanced for the rarity of this complication of pregnancy is that, statistically, rheumatic fever is a disease of childhood and adolescence rather than of maturity. Hence, recurrences are less likely to take place. Hamilton<sup>6</sup> points out that the average age at the time of the first attack of rheumatic fever is 13½ years, whereas the average age of pregnant cardiac patients is 27 to 28 years. This is in accord with our own experience.

The occurrence of rheumatic fever in a primipara with mitral stenosis at term posed two interesting problems: its effect on the mother and baby and its effect on the management of labor. There is considerable divergence of opinion as to the effect of infection on prognosis in cardiac obstetric patients. Some feel that infection is more likely to be the final insult to a failing heart, while others state that it is the prime factor in severe failure and death. The patient described above was treated for rheumatic fever in the usual manner and labor was allowed to proceed in a normal fashion. After delivery, prolonged bed rest was given and resumption of activity was permitted only when all signs of infection had subsided, and the general physical condition warranted it.

In Schaeffer's patient,<sup>4</sup> as reported above, the baby developed polyarticular arthritis associated with fever, three days after birth and ran a stormy course for the next six weeks. He felt that this was due to intrauterine infection, though it seems possible that it might have contracted the disease from the mother postnatally. The other authors made no note of rheumatic infection in the child, and the baby in our case has remained healthy.

### REFERENCES

- (1) *Bramwell, C., and Longson, E.*: Heart Disease and Pregnancy, London, 1938, Oxford University Press, p. 99.
- (2) *MacKenzie, J.*: Heart Disease and Pregnancy, London, 1921.
- (3) *Jensen, J.*: Personal communication.
- (4) *Schaeffer, A.*: Berl. klin. Wchnschr. 23: 79, 1886.
- (5) *Heffernan, E. B.*: Med. J. Australia 1: 608, 1922.
- (6) *Hamilton, B. E.*: Am. Heart J. 14: 555, 1937.
- (7) *Jensen, J.*: The Heart in Pregnancy, St. Louis, 1938, The C. V. Mosby Co., p. 212.

326 ST. JOHNS PLACE  
855 PARK PLACE

## MASSIVE CONDYLOMATA ACUMINATA OF THE VULVA COMPLICATING LABOR

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**M**ASSIVE condylomata acuminata of the vulva complicating labor have rarely been reported. This unusual association was seen recently in two instances and is being reported because of the unexpected favorable response of the vulval tissues during the second stage of labor. Search through the literature has revealed only three such cases.<sup>1-3</sup>

Striking similarity in the clinical picture can be noted in these three cases. In each, the lesions were massive; grew rapidly during pregnancy and were widely distributed about the vulval tissues. All three patients were at term. One patient, allowed to deliver spontaneously, died of sepsis. Two were delivered by cesarean section, but in only one was the presence of the condylomas the indication for surgery.

In the one instance of spontaneous delivery,<sup>2</sup> an attempt was made to deliver the patient by forceps. Due to the difficulty encountered in applying the forceps, this method was abandoned, and the patient was finally allowed to deliver spontaneously. No episiotomy was performed and there were no lacerations. On the third day post partum, the patient developed a chill, and fever of 103° F. On the fifth day she died of acute peritonitis and generalized sepsis.

One patient<sup>1</sup> was delivered by cesarean section because of the presence of the vulval lesion. This patient ran a febrile course for forty-seven days following delivery, but eventually recovered. The condylomata acuminata were later excised.

The second patient<sup>3</sup> who had a cesarean section was delivered abdominally because of four previous sections and cephalopelvic disproportion. Here, the lesion was excised one month prior to delivery, and at the time of delivery the vulva was well healed. The post-partum course was uneventful.

### CASE REPORTS

**CASE 1.**—R. C., a 16-year-old, colored nullipara, was admitted to the service of Dr. Charles A. Gordon on Dec. 9, 1939. Her last menstrual period was May 15, 1939. Four months prior to admission the patient noted a "red rash" over the entire vulva, which itched almost continuously, and was associated with a thick yellow vaginal discharge. The roughened area increased in size, and rapidly assumed the character of a dense warty growth. In November, 1939, she attended an obstetric clinic where she was given expectant and palliative treatment, but because of the rapidity of the growth she was later admitted to the hospital.

The Wassermann and gonococcal complement fixation tests were negative, although her husband was said to have had "trouble with his blood," and had received intermittent treatment. Dark-field examination of the lesion was reported as "Spirochaeta resembling pallida." A biopsy taken Nov. 2, 1939, showed dyskeratosis and hyperkeratosis. Three days after admission, the patient was transferred to another hospital for contagious diseases where she remained until Dec. 8, 1939, when she signed her release. Smears for gonococci were negative as was the Wassermann test. The lesion was diagnosed as condylomata acuminata. The following day, the patient noted an escape of fluid from the vagina and applied for admission to the Kings County Hospital.

Examination of the abdomen revealed a seven and one-half months' pregnancy. The position was L.O.A. and the head was floating. The fetal heart was normal. The vulva was covered by a dark brown, profusely distributed, foul-smelling, warty growth. The clitoris was hypertrophied, bulbous, and inflamed. Condylomas involved both labia majora, which were congested and edematous, and

The pathologic report was as follows:

A. A resected tube. Almost the entire tube except for the distal quarter had been expanded to form a sac approximately 7 cm. in diameter. At one point the sac presented a perforation forming an opening into the lumen  $2\frac{1}{2}$  cm. in diameter. This led into the cavity of an amniotic sac of a placenta firmly adherent to the inside of the dilated tube. Attached to the placenta was an umbilical cord approximately 15 cm. in length. This remained attached at the other end to a well-formed and normal-appearing fetus, measuring approximately 7.5 cm. from crown to rump. The head of the fetus lay within the tube, the opening of which (described above) was about the neck of the fetus. The remainder of the fetus had passed through the perforation of the tube and lay external to the tube.

B. A fetus measuring approximately 15 cm. from crown to rump, the extremities being disposed in a typical folded manner. All the tissues had a hard, woody consistency. Numerous fibrous and fibrofatty adhesions were attached over the surface of the body. No umbilical cord was present. The right auricle was distinguishable. The facial features were masked, as if by a veil of tissue incorporated with and covering the face. The limbs were somewhat distorted and misshapen. The left foot had been amputated at the tarsus; it was present just above the left elbow where it was adherent though slightly movable.

A summary of a careful review of this patient's entire menstrual history indicated that her menstruation had commenced at the age of 13, and recurred regularly every thirty days with a moderate flow, lasting four days, without pain. Her initial sexual contact had been at the age of 26 (four years before) and the next menstrual period was three days late. With the exception of the amenorrhea during her one normal gravidity, this was the only delay recalled by the patient. There was, then, no period of amenorrhea to correspond with the intra-abdominal pregnancy, nor were there any symptoms.

In this case, there is a coincidence of a lithopedion and subsequent intrauterine pregnancy, and an extrauterine pregnancy subsequent to that, with rupture (and incidental discovery of the lithopedion). The other tube was completely normal. The lithopedion was free in the abdominal cavity, adherent to the omentum. There was no trace of placenta. We have here the coincidence of an abdominal calcified pregnancy, and intrauterine pregnancy, and extrauterine pregnancy, offering, as far as we know, a unique combination. The age of the lithopedion can only be inferred, since there are absolutely no symptoms in the history, no period of amenorrhea to correspond with a pregnancy. The date of conception of the intrauterine pregnancy which anteceded the ruptured ectopic was fourteen months before admission to the hospital. It is conceivable on the basis of time and the complete absence of any previous period of amenorrhea, that we are dealing with a combined as well as a compound pregnancy, that is, that the abdominal pregnancy and intrauterine pregnancy were simultaneous. This is a difficult thing to prove in the absence of any history of pain or untoward incident during the course of the intrauterine pregnancy, and in view, perhaps, of the degree of condensation of the lithopedion.

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1 WEST EIGHTY-FIRST STREET

Numerous laboratory tests were done and cultures taken. These were all negative except for one uterine culture, which revealed *streptococcus hemolyticus*. Wassermann tests on two occasions were negative, as were numerous smears for gonococci.

CASE 2.—M. J., an 18-year-old, colored nullipara, was admitted to the service of Dr. Charles A. Gordon on Aug. 9, 1940. Her last menstrual period was Dec. 31, 1939. Three months prior to admission she first noted the presence of "warts" about the vulva, which progressively and rapidly increased in size. She experienced itching of the vulva and burning on urination soon after the growths were noted. Labor pains began on August 8, one day before admission.

Examination of the abdomen revealed a seven and one-half months' pregnancy. The vertex was presenting, the fetus active, and the fetal heart was normal. The labia majora were covered by three large, and other numerous smaller protruding cauliflower-like growths. Two of the large lesions occupied the lower one-half of both labia majora. The largest lesion measured  $1\frac{1}{2}$  by  $\frac{3}{4}$  by  $\frac{1}{2}$  cm. The lesions were pinkish, vegetative, moderately firm, nontender, and the surface showed numerous papillae. Several small condylomas were distributed about the anus and in the fold between the thigh and labia majora on the right. The large lesion on the left extended to, and covered a part of the perineum.

The Wassermann test was negative. Vaginal smear showed many pus cells and a gram-negative diplococcus resembling the gonococcus. A biopsy of the lesion was reported as "Condylomata acuminata with subacute and chronic infection."

After twenty-two hours of labor the patient was delivered spontaneously of a four-pound eleven-ounce, living, male infant. The duration of the second stage was thirty-two minutes, and the third stage ten minutes. During the second stage, distention of the vulva and perineum progressed normally and appeared to be little affected by the lesions. The tissues involved by the growths stretched easily and did not lacerate.

The post-partum course was febrile, fever of  $102.2^{\circ}$  F. occurring on the second day post partum, and the highest temperature of  $103.4^{\circ}$  F. on the eighth and ninth days post partum. The temperature was normal on the eleventh day, and she was discharged on the twelfth. Sulfanilamide was given between August 11 and 17 (the dose grains xx every four hours). Her general condition at the time of discharge was good.

#### REFERENCES

- (1) Prochorow, S. N.: Zentralbl. f. Gynäk. 53: 1002, 1929. (2) Sorrentine, B.: Riforma med. 47: 980, 1931. (3) Phaneuf, Louis: Am. J. Surg. 13: 468, 1931.

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Holland, E. E.: Ophthalmia Neonatorum, J. Indiana M. A. 33: 236, 1940.

Fifteen per cent of the inmates of the Indiana State School for the Blind have a clear history of ophthalmia neonatorum. The best way to prevent the disease is to instill a few drops of fresh 1 per cent solution of silver nitrate in the baby's eyes as soon as possible after delivery.

If pus appears in a baby's eyes, a culture and smears should be made. If the gonococcus is present, the baby should be hospitalized and if possible placed under the care of a competent ophthalmologist. A baby with ophthalmia neonatorum should never be treated at home, because the constant and skilled attention of a properly trained nurse is absolutely necessary.

Sulfanilamide in 2 gr. doses every four hours for three days has been used with good success. Foreign protein, given intramuscularly to raise both the body temperature and the antibody titer, may be used with some benefit.

In these cases minutes are precious. A day may mean the difference between sight and blindness.

J. P. GREENHILL.

extended from about 1.5 cm. from the anterior fourchette downward to the anus, which was almost encircled. The lesion was 3 cm. in thickness in its area of greatest development. The width of each labia was 2 cm. and the length 15 cm. The growths were nontender, friable, and bled easily. The labia minora were not involved (Fig. 1).

Rectal examination revealed an uneffaced, closed cervix. The vertex presented and was not engaged. The rectovaginal septum was somewhat resistant and thickened.

Labor began at 6:15 P.M. Dec. 10, 1939, one day after admission. The duration of the first stage was five hours and thirty-five minutes. Vaginal examination at this time revealed the posterior wall of the vagina to be coarse, granular, thickened, and rather inelastic, although it could be depressed somewhat. The cervix was fully dilated and the membranes intact. There was moderate resistance to the advancing head. No episiotomy was done because of the danger of infection and bleeding, which might result from the necrotic and congested tissue. The membranes began to bulge at 11:50 P.M., and were ruptured artificially. As the presenting part reached the introitus, an effort was made to control the rapidity of its



Fig. 1.—Case 1. External view of condylomatous masses.

descent. The head was allowed to stretch the vulval tissues gradually while the elasticity of these structures was observed. It was seen that the stretching of the labia and perineum was normal in all respects, and at no time did there appear to be any danger of laceration. The lesion appeared to have no significant effect on the delivery of the infant. A four-pound ten-ounce female infant was delivered at 11:58 P.M. The placenta was expelled spontaneously, intact, seven minutes later. There was no gross pathology of the placenta noted, bleeding was minimal, and there were no lacerations. Duration of labor was five hours and fifty minutes.

Following delivery, the patient's temperature fluctuated between 99.4° and 103.4° F., the highest temperature occurring on the sixth day post partum. The patient was put on a course of sulfanilamide, receiving a total dose of 15 Gm. The temperature fell to normal on the tenth day where it remained until the patient was discharged.

Following delivery, the growth reduced markedly in size, but the odor and necrotic nature persisted.



pounds and 3 ounces, was removed and resuscitated with the Drinker respirator and B. and J. inhalator. As soon as the baby was removed, the sac which had contained the baby collapsed. The patient immediately went into shock. Anesthesia was stopped. Oxygen was administered along with emergency treatment of the shock before the operation could proceed. Removal of the baby permitted a more careful examination of the abdominal pathology. The uterus was in relatively normal position, about three times the normal size, and uncomplicated by adhesions. The right tube and ovary were normal. Both round ligaments were greatly hypertrophied and found in their normal locations. The gestation sac was not densely adherent to the surrounding intestines. There were several fine adhesions between the descending colon, sigmoid, and posterior surfaces of the sac. Several fine adhesions were located between the loops of the small intestines and the posterior surface of the sac. All of these adhesions were easily separated with the fingers and scissors. The sac occupied the location of the left ovary. The left ovarian ligament arose from the sac and was attached to the body of the uterus. The left tube was identified adherent to the anterior surface of the sac and intact in its entire length. The left infundibulopelvic ligament was greatly enlarged by the blood vessels which carried the main blood supply to the fetus. Many of these vessels were a centimeter in diameter. The sac was thin, not more than a few millimeters in thickness, with the placenta attached to its posterior, left, inner surface. Removal of the left adnexa was comparatively simple.

Postoperatively the patient required immediate treatment of her acute shock. She had a morbid course for two weeks. She was discharged on the nineteenth post-operative day in good condition with a living child.

The pathologist's report was as follows: "Placental sac: This is a ruptured sac which is about the size of a basketball. The placenta basalis and umbilical cord are attached to the inside of the sac. The infundibulopelvic ligament and ovarian ligament are attached to the outside. The tube can be demonstrated by inserting a hemostat through its lumen. Biopsy from sac and placenta (microscopic examination): One section shows typical chorionic villi and syncytial cells. There are small areas of coagulation necrosis. The other two sections show connective tissue in which there are bundles of smooth muscles, arterioles and venules. No ovarian tissue is demonstrable. One of the sections contains a cross-section from the isthmus of the oviduct. The lumen is small. The mucosa is folded and lined with simple columnar epithelium. The wall contains the usual smooth muscle fibers. Diagnosis: Extra-uterine pregnancy, ovarian."

The follow-up examination on Nov. 14, 1939, revealed a normal multiparous pelvis except for the absence of the left adnexa and the presence of a small cystic mass in the cul-de-sac which was not tender and was believed to be a resolving hematoma.

## DISCUSSION

The criteria of ovarian pregnancy as designated by Spiegelberg are: (1) The tube on the side of the pregnancy must be intact. (2) The fetal sac must occupy the position of the ovary. (3) The pregnant ovary must be connected with the uterus by the uteroovarian ligament. (4) Definite ovarian tissue must be found in the wall of the sac. This specimen grossly complied with these stipulations. Microscopically it was impossible to find ovarian tissue in any of the several pieces examined. This case bears out the statement of Norris and Mitchell:<sup>30</sup> "12 highly probable cases are at term, which is interesting in illustrating the greater distensibility of the ovary over the tube. . . . The great growth of the fetus destroys the relations and obliterates normal tissue to such an extent that the fulfillment of all of Spiegelberg's criteria is quite difficult." The thinning of the sac in my patient was probably the cause of failure to find the ovarian tissue.

## OVARIAN PREGNANCY WITH LIVING CHILD AND MOTHER

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THE purpose of this paper is to report an ovarian pregnancy which went beyond term and resulted in a living baby and a living mother. According to the available literature, 38 cases of ovarian pregnancy have gone to the age of viability (seven months) or beyond. Of these 38 cases, 12 resulted in living babies and 22 resulted in living mothers. In 8 cases both mother and baby lived.

Cuthbert Lockyer (1917) in accounting for the discrepancies in accepted and reported cases of primary ovarian pregnancies up to 1909 noted that Norris (1909) adopted the English standard of excluding cases published before that of Van Tussenbroeck (1899) and explained that this standard was not followed by the German writers. The German and American estimates of the total number of ovarian pregnancies up to 1909, therefore, vary from 8 to 2.

Mrs. M. F., colored, aged 41 years, had been married twenty years and had had 4 full-term pregnancies with uncomplicated spontaneous deliveries. She had received prenatal care for this pregnancy (fifth) at The King's Daughters' Maternity Center where several medical students had recognized an abnormal enlargement of her abdomen, and in the latter part of her pregnancy had made these diagnoses: "fibroids, multiple pregnancies, placenta previa, and transverse lie." The course of this pregnancy had been symptomatically uneventful except for a small amount of vaginal bleeding on Jan. 21 and 22, 1939. Her last menstrual period was Nov. 25, 1938. Her expected date of confinement was Sept. 1, 1939; and on account of extreme abdominal enlargement and failure to begin labor, she was admitted to another hospital on Sept. 9, 1939 for observation. Following an x-ray and several days' stay in the hospital she was discharged undelivered.

On Oct. 4, 1939, I saw her for the first time when she was admitted on my obstetrical service at the Norfolk General Hospital after having been in abnormal labor for eighteen hours. On admission she was complaining of abdominal tenderness, intermittent, irregular, abdominal pain; but there was no vaginal bleeding or discharge. Abdominal examination revealed a greatly distended thin-walled abdomen, the height of the fundus to be 33 cm., and a suprapubic fullness that arose perpendicularly from the pubic bone for about 14 cm. and then extended upward toward the fundus of the uterus. The abdomen was tense and felt cystic. The tenderness was diffuse. No uterine contractions were present. The fetal head was palpable in the right iliac fossa, but due to the extreme tenderness and distention, the soft parts of the baby were indeterminate. Fetal heart sounds were heard in the left lower quadrant and over the entire lower abdomen. No vaginal examination was made. The rectal examination revealed an irregular mass high in the pelvis which had no connection with the fetal head. It was impossible to outline the cervix. External pelvimetry was that of a normal gynecoid pelvis. X-ray examination following admission showed a full-term pregnancy, head not engaged, face presentation, and brow in the right iliac fossa. The patient was prepared for immediate cesarean section with preoperative diagnosis of postmature pregnancy, face presentation, and suspected abdominal pregnancy.

The abdomen was opened by a midline incision from the pubis to the umbilicus. Upon opening the peritoneal cavity a moderate amount of brownish green fluid escaped. The nonpregnant uterus occupied the suprapubic area, extended vertically, and was about the size of a two and one-half months' gestation. A mass filled the entire abdominal cavity. Its bluish gray surface contained large tortuous veins. The wall of the tumor was found to be extremely thin when it was opened by an incision about six inches in length. A postmature normal male infant, weighing 10

## FETUS COMPRESSUS DIAGNOSED BY X-RAY

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**A**MONG the rarely noted instances of this anomaly, the case reported by Kerr and Rypins<sup>1</sup> is the only instance in which x-ray evidence of the presence of fetus papyraceus was obtained before delivery. In their case, the patient delivered spontaneously and expelled a compressed fetus which appeared to have approximated the age of the living child.



Fig. 1.

### CASE REPORT

Mrs. G. H., a 24-year-old primipara, was admitted to the hospital at term. The diagnosis of breech presentation had been made earlier in her pregnancy, but an attempt at external version had been unsuccessful. Her past history was negative. The pelvis was of the android-gynecoid variety but was judged adequate for a baby up to 8 pounds. Labor had begun spontaneously at home with the membranes intact. Pains on admission were every five minutes, but the breech was high so a rectal examination was not done. The labor during the next twelve hours was characterized by long intervals of five- to seven-minute pains which were strong enough to have engaged the breech. A vaginal examination revealed a cervix that barely admitted two fingers and was thick and tough. The palpating fingers came against an uneven rather rough surface with tiny sharp points placed

## FETUS PAPYRACEOUS

### TRIPLET PREGNANCY, WITH ONE NORMAL AND TWO PAPYRACEOUS FETUSES

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PATIENT, aged 29 years, was delivered of her first baby by one of us (O'R.) in 1938. There was nothing remarkable about her ante-partum course. She had a normal delivery of a 3,650 Gm. male child. Post-partum course was normal.

She returned in the spring of 1940 in the second month of her second pregnancy. Her general condition was good, her serology negative, and she ran a perfectly normal prenatal course. There was nothing to make one suspicious of a multiple pregnancy.

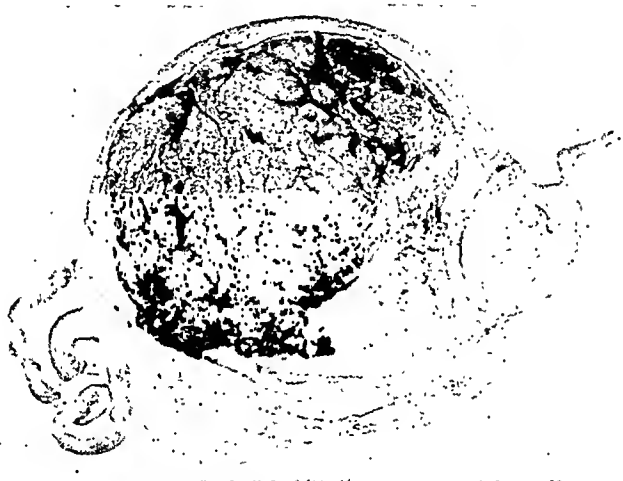


Fig. 1.—Showing second papyraceous fetus embedded in amniotic sac of normal fetus.

Three weeks before her estimated date of confinement, she went into labor. She came to the hospital where one of us (C.) found a mass protruding from the vulva. A fetus papyraceous was delivered, which apparently had died between the fourth and fifth months. The only evidence of cord was a small dried-up string-like structure. Following this delivery, the labor stopped, the cervix contracted to about 2 cm. dilatation. As the uterus did not seem very large, it was thought advisable to let the normal fetus develop further, so the following day the patient was sent home.

Nine days later, the patient returned in active labor and after eight hours was delivered of a normal 3,400 Gm. male baby.

Examination of the placenta and membranes revealed a second papyraceous fetus embedded in the amniotic sac close to the placenta. The patient made an uneventful recovery.

Dr. Herbert Traut, who made the pathologic report, said this was a biovular fetation and suggested this abnormality may be more common than generally suspected, due to the fact that papyraceous fetuses may be missed if the amniotic sac is not carefully inspected, especially if fetus dies early.

# Special Article

## THEOPHILUS PARVIN

### AN IMPORTANT INFLUENCE IN AMERICAN OBSTETRICS AND A PIONEER IN CLINICAL TEACHING

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"NO MAN in either hemisphere has been more widely recognized for his contributions to the subject of Obstetrics," says G. C. Mosher of Theophilus Parvin, whom he styles The Apostle of Casuistry in Medicine. Whether or not this statement may be debated, this author's appraisal of this important American obstetrician is stimulating and revelatory. Theophilus Parvin will be remembered in historical annals for at least two significant achievements, his authorship of an obstetric text which is remarkable for its sound doctrine and literary style, and his pioneer role in establishing in America the hospital instruction in obstetrics for medical students.

A survey of Parvin's *Science and Art of Obstetrics*, published in 1886, impresses one with the truth of a biographer who said that it "teemed with the characteristics of the man." In appraising his work, however, we are at once reminded that the author lived in a period of this country's history which in its writings and on the lecture platform was marked by a rhetorical splendor which, in spite of its extravagance, reflected a good deal of the spirit of that age. We are apt to smile at the ciceronian efforts of some of the medical orators of that day, but there is little doubt that could we have sat at the feet of a Meigs or a Parvin we would have attended with the same enthusiasm and acclaim as did our fathers. Such men as these did more than excel in the art of oratory, for they have left evidence that they were also excellent teachers of clinical medicine and possessed a knowledge of pedagogics which their medical descendants have too greatly ignored.

W. H. Parish says of Parvin that his acquaintance with the literature of obstetrics was probably unsurpassed by any of his contemporaries, and this is not difficult to believe for his writings reflect an erudition truly remarkable. His familiarity with the writings of the ancients as well as with The Bible and The Talmud are greatly in evidence. Although a profound literary stylist, his works show much original thinking which manifests itself in sound and at times prophetic doctrine. An understanding of this may be gained from noting some observations in his obstetric text. In discussing the bony pelvis he states that "in some instances the points of difference are so slight that it is very difficult to decide whether a pelvis is male or female," a point long recognized by anthropologists and forgotten by many medical writers since his time. His care of the prenatal patient sounds a familiar modern note, for he recommends that, "The obstetrician should visit the preg-

at intervals (later found to be the rib margins of the compressed fetus). It was decided that further examination might make an abnormal situation worse and that an x-ray was in order.

A radiographic examination (Dr. Parmelee) of the abdomen shows a full-term fetus in utero in a frank breech position. In addition it was possible to identify another fetus, of approximately four months in size, lying transversely beneath the breech of the first fetus and across the cervix. The maternal pelvic development was normal and the dimensions of the pelvic inlet within normal limits except for a rather flat sacrum and, therefore, narrow posterior pelvis.

A low transverse cervical cesarean section was done under nitrous oxide-oxygen-ether anesthesia, and a normal female infant weighing 6 pounds 2 ounces was delivered. The compressed fetus was found to completely cover the internal os of the cervix much like a central placenta previa and was removed with the secundines. It possessed its own placenta and membranes, the former adhered to the margin of the normal placenta. The membranes could not be clearly differentiated and were loosely adherent to the outer margin of the right arm and leg of the compressed fetus. The cord was wrapped once about the right arm and leg. Both patient and baby are doing nicely.

There was no indication during this patient's ante-partum course of the presence of any abnormality and her general condition was excellent.

#### REFERENCE

- (1) *Kerr and Rypins*: Am. J. Roentgenol. 28: 89, 1932.
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Menendez, Orta: Postabortive Tetanus, Rev. Cubana de obst. y ginec. 1: 89, 1939.

A fortunately rare complication of criminal abortion is tetanus. A young woman three and one-half months pregnant was aborted at home by the use of sound and curette. The following day chills and fever appeared. There was a slight show of blood. Another curettage was done and ice packs were applied to the abdomen. On the seventh day after the first intervention, the patient noted pain on chewing or turning the head. General malaise, headache, and fever ensued. Three days later she could not open her mouth.

On admission to the hospital the patient was opisthotonic, with tonic and clonic convulsions. Avertin was administered per rectum and a gauze pack saturated with antitetanic serum, inserted into the uterus alongside a catheter. Through the latter 3,000 units of tetanus antitoxin were instilled hourly and irrigations of oxygenated water were given for ten days. The gauze was changed daily. The tube was removed the tenth day. Tetanus antitoxin was given in large doses intraspinally, intravenously, and intramuscularly. Avertin, 6 to 8 Gm., was administered, divided into a morning and afternoon enema. The patient was nourished by vein and nasogastric tube.

Three days after admission, the convulsions became less frequent and were gone by the eighteenth day, on which the mouth could be opened slightly. On the twenty-fifth day, the patient could take nourishment by mouth.

R. J. WEISSMAN.

essayist and philosopher, that arrayed in these glories, crowned with these honors, we almost forget that he is a physician and medical teacher, once by his bold decisive utterances, his startling array of facts, his invincible logic, greatly contributed to destroy a pernicious doctrine taught by some of our leading obstetric authors—a doctrine which was more certainly laden with death than the foul wind that was destroying the citizens of Agrigentum."

Among the writings of Parvin we should not overlook his *Lectures on Obstetric Nursing*, a small work of less than 100 pages and a medical classic. This work was originally two lectures which the author gave for nurses at the Philadelphia Hospital. Here again his views regarding asepsis and antisepsis and the control of puerperal fever show real vision for his time. He emphasizes the value of the nurse making prenatal visits to her patient and recognizing untoward signs and symptoms so that they may be reported. Indeed, so much of Parvin's thought has not been outmoded by present-day opinion that the republication of this little volume would be a useful enterprise.

The pioneer role of Theophilus Parvin in the teaching of clinical obstetrics in hospital practice is shown in his address before the American Academy of Medicine in New York in 1888. This is entitled "The Necessity for Practical Obstetrics in the Course of Instruction Given by Medical Schools." Here he states that he was made conscious of the great deficiency in the American plan of obstetric instruction while on a visit to Munich where he had observed the teaching of Winckel. He presents a detailed account of Winckel's method as observed by J. Clifton Edgar, who for five months was resident obstetrician at the Munich Frauenklinik. This account is important aside from its historic interest because of its application to the present-day problems of clinical teaching. Speaking of the actual practice of each student before graduation in Munich he writes:

"In the first place, he is required to attend the Obstetrical Clinic two semesters (winter five months, summer four months). Supposing he is called down in this clinic every two weeks, in that case he would touch (thoroughly examine externally and internally) eighteen gravid or parturient women. This is a low estimate. At the very lowest estimate, then, the student must have examined eighteen gravid or parturient women and conducted four labor cases, and taken the operation course on the phantom for one semester. The majority of students who come up for State examination in Munich have also taken a private 'touch course.'

"In one of these courses, extending over five months (one semester), each student, at the very lowest estimate, examines both externally and internally, and each case several times, not less than forty cases. This course is not prescribed by law. My friends among the recent graduates in Munich informed me that the majority of students take one or more of these 'touch courses.'

"Many students also see and conduct more labor cases than are prescribed by the State. Thus, for example, a German friend, recently graduated, informed me that while a student he conducted ten cases of labor in the clinic, and he did not seem to think he was getting more than his share.

"Many students serve during vacation in what is known as the Polyclinic. Here they are called to abnormal cases of labor that may occur in the city, and in this way they see many additional cases."

In commenting upon these statements Parvin points out that the vast majority of American medical students are graduated without ever having witnessed, still less had charge of, a case of labor. The remedy, he states, lies in the practical teaching of obstetrics being directly associated with its scientific instruction . . . in other words there should

nant woman from time to time, especially during the latter weeks of pregnancy, so that he may know her condition is favorable for her approaching trial. Once a week during her last two or three months of gestation, the urine should be examined with reference to possible albuminuria." Regarding anesthesia he quotes a European authority speaking of nitrous oxide oxygen, "it can be inhaled for hours without any bad results. In most cases its results were entirely satisfactory, but in some it produced temporary violent excitement." Parvin also recommends elective cesarean section, recognizes the usefulness of episiotomy, and



*Theophilus Parvin*

was far advanced for his day in his knowledge of the etiology and treatment of puerperal sepsis. In 1885 he actually experimented with the local application of a solution of 4 per cent cocaine to effect local anesthesia. The results were negative, however.

An example of Parvin's oratorical style is seen in his tribute to O. W. Holmes in his address at the International Medical Congress in 1876. He writes, "Empedocles combined in one, poet, priest, politician and physician; and history records that he rescued a city from desolation by blocking up a mountain gorge through which pestilential winds were sweeping. In like manner an American whom the world knows as poet,



his subject. I know of no other text of his time which is so fraught with lessons for today or which can be more useful to the student who wishes to attain a knowledge of the fundamental background of modern obstetrics.

The facts of Parvin's life are readily available in the usual sources of biography, but it may be useful to repeat some of them here.

Theophilus Parvin was born in Buenos Aires on Jan. 9, 1829. His father, of the same name, was a missionary to the Argentine Republic, having prepared for the ministry at the University of Pennsylvania and the Princeton Theological Seminary. His mother was the daughter of Caesar Augustus Rodney, one time Attorney-General of the United States and later Minister to the Argentine Republic. Parvin's mother died when he was an infant and his father brought him to this country. At the age of seven the father died and the boy went to live with a guardian, the Rev. Dr. Steel of Abington, Pa. When twelve years of age Parvin entered the preparatory department of Lafayette College and later entered the University of Indiana from which he received his bachelor's degree in 1847. For the next three years he taught at the Lawrenceville High School at the same time studying Hebrew and Greek at the nearby Princeton Theological Seminary. In 1850 he received his master's degree from the University of Indiana and in 1852 his medical degree from the University of Pennsylvania. He became an interne at the Wills Eye Hospital in Philadelphia and later a ship surgeon on a packet line sailing between Philadelphia and Liverpool. He then settled in Indianapolis where he practiced until the close of the war. In 1864 he was elected to fill the Chair of Materia Medica in the Ohio Medical College, and in 1869 he resigned to accept that of Obstetrics and Diseases of Women at the University of Louisville. In 1876 he accepted a similar chair in the College of Physicians and Surgeons of Indianapolis and two years later became Professor of Obstetrics, et cetera, at the Medical College of Indiana. In 1882 he was recalled to the chair previously held by him in the University of Louisville. The next year he was called to the Chair of Obstetrics and Diseases of Women and Children at Jefferson Medical College, Philadelphia.

During his professional life many honors came to Theophilus Parvin, among which may be numbered the Presidency of The American Medical Association, of The American Gynecological Society, of The American Academy of Medicine and The Philadelphia Obstetrical Society. In addition to the writings mentioned above, he translated *Winckel's Diseases of Women* and wrote for *Ashurst's Encyclopedia of Surgery*, *The American Textbook of Obstetrics* and *The American Textbook of Applied Therapeutics*. Other of his important accomplishments could expand this all too brief outline into greater proportion, for Parvin's life was one of intense activity and fulfillment. In his obituary, which appeared shortly after his death in the *Journal of the American Medical Association*, we find this note which tells its own story of affliction and personal courage:

"About eight years ago when examining a patient he inoculated his index finger with specific poison, and recognizing the nature of the affection he called the attention of the class to it on several occasions as a warning to them to be always on their guard. His health subsequently became impaired and he suffered with a severe form of chronic laryngitis which compelled him for a time to suspend his lectures; of recent years, however, this affliction had been overcome so that he not only resumed his course of lectures, but was able to accept complimentary invitations to address medical societies."

be a maternity belonging to every medical school in which practical obstetrics is taught. It was through the effort of Theophilus Parvin that the trustees of Jefferson Medical College in 1886 authorized the establishment of the first maternity department in any American hospital and assigned three rooms for the purpose. Work was begun in February, 1887, and at the time of his writing thirty-four women had been successfully delivered, the ward classes having been instructed by Parvin's assistant, Dr. William E. Ashton. In November, 1887, because of lack of room in the hospital, the out-patient department was established where clinical instruction was also carried out. In his peroration he states, "May the time soon come when every medical school which does not take this step, and make this necessary reform, shall perish under the common and condign, popular and professional damnation." At a later date, as President of The American Gynecological Society and speaking on the same subject, he sounded this prophetic note, "The true ideal can only be realized in a large hospital devoted to obstetrics and diseases of women, students being taught in a small number at a time."

Interesting to us in this latter address are Parvin's comments on the use of the word Gynecology, because much confusion still exists as to its correct usage.

"Let me, by an appeal to etymology," he states, "rescue gynceology from its narrow use, . . . gynceology should be regarded as a synonym for obstetrics rather than for diseases of women, and the gynceologist is primarily an obstetrieian. . . . The word gynceology, both etymologically and in its essential signification, relates to reproduction in the human female, and secondarily to the diseases and disorders which interfere or prevent this function, or those which are consequent upon its exercise."

It is also important to remember Parvin's significant part in the union of obstetrics and gynecology as branches of medical instruction. In this he was ably supported by the opinions of Winckel to whom he had written for advice on the subject. Space does not permit an account of the conclusions of this eminent European teacher, but his views on the subject cannot be overlooked by those who, even today, do not favor such amalgamation in hospital practice or for purposes of clinical instruction.

Mosher refers to Parvin as "The Apostle of Casuistry," and by this he interprets "Casuistry," as did Parvin, in its original classical meaning, the application of ethical principles to questions of conscience and judgment. It is probable that no modern medical writer so concerned himself with this aspect of medicine as did Theophilus Parvin. Throughout his writings we are impressed with his sound logic concerning the difficult problems that are so often associated with the forming of medical opinion. An example of his manner is seen in his discussion of the diagnosis of pregnancy.

"Ambition to give a prompt decision," he writes, "or pride in opposing that of another, may lead to error. Rapidity is very far from proving correctness of diagnosis; here, as Lord Bacon has said of another matter, our intellects need not wings but weights of lead to moderate their course. The man of greatest knowledge least exalts his attainments, and is the most cautious and deliberate in judgment, and has respect for the opinions of others. Sloth may hinder or prevent our thorough investigation. We may be satisfied with a few facts instead of seeking all that are available."

Such excerpts from the writings of Theophilus Parvin tell us something of the man, but only in his *Science and Art of Obstetrics* do we realize the lofty spirit and broad clinical knowledge that he brought to

# Department of Maternal Welfare

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CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

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## MATERNAL MORTALITY, 1939

EDWIN F. DAILY, M.D., WASHINGTON, D. C.

*(From the Division of Maternal and Child Health, Children's Bureau,  
U. S. Department of Labor)*

THE lowest maternal mortality rate ever recorded in the United States, 40 per 10,000 live births, has been reported by the Bureau of the Census for the year 1939. The maternal mortality rate for all causes decreased 9 per cent during 1939 (from 44 per 10,000 in 1938 to 40 per 10,000 in 1939). The maternal mortality rate for 1939 was 32 per cent lower than that for 1934, before the initiation of a nation-wide program of health services for mothers and children under the Social Security Act. This is a much larger gain than was attained in the five years before the Act was passed. From 1930 to 1934 the maternal mortality rate for the United States dropped only 12 per cent. The death rate for all causes for persons of all ages has decreased only 5 per cent since 1934.

A total of 9,151 women died in 1939 from conditions of pregnancy and childbirth; 6,995 of these women were white, 2,083 were negro, and 73 were of other races. The maternal mortality rate for negro women (77) was more than double the rate for white women (35). The mortality rates for both white and negro women have decreased in recent years, but the decrease has been much greater among the white than among the negro.

Maternal mortality rates varied from a low of 22 in Idaho to a high of 65 in Florida (see Table I).

The majority (5,613, or 61 per cent) of the 9,151 women whose deaths were classified as maternal in 1939 died during or after childbirth; 24 per cent (2,160) died following abortions or ectopic gestation, and 15 per cent (1,378) died undelivered (see Table II). Childbirth in the 1938 revision of the International List is defined as the termination of a uterine pregnancy after seven lunar months (twenty-eight weeks or more) of gestation. Abortion is defined as the termination of a uterine pregnancy before seven lunar months (twenty-eight weeks) of gestation.

The pregnancies of 1,786 of the 2,160 women who died after abortion or ectopic gestation were uterine pregnancies, and 374 were extrauterine. The abortions of 220 women were stated to have been self-induced and those of 157 to have been criminal.

More than 70 per cent (990) of the 1,378 women who died undelivered died from toxemias of pregnancy. Only 61 died from hemorrhage. For almost one-fourth (327) of these deaths, the physician gave no real information as to the cause, but merely entered the fact of pregnancy or that the mother died before the baby was born.

Infection was responsible, in all, for 42 per cent (3,834) of the 9,151 deaths. More than 60 per cent (2,353) of the women who died from this cause died during or after childbirth, but 1,393 died after abortion and 88 from ectopic gestation.

Toxemias of pregnancy were responsible, in all, for 24 per cent (2,232) of the 9,151 deaths. Slightly more than one-half (1,149) of these 2,232 women died during or after childbirth; 990 died before delivery and 93 after abortion.

Like his distinguished contemporaries, Hodge and Meigs, Parvin's life as a physician and teacher was one of great fulfillment. To the field of obstetric science he brought a maturity of mind and keenness of vision which reflected itself in his writings and teachings. It was fortunate that the advent of scientific obstetrics in America had among its followers so great a champion as Theophilus Parvin.

" 'Tis man's worst deed  
To let the things that have been, run to waste  
And in the unmeaning Present, sink the Past."

## REFERENCES

- (1) *Parish, W. H.*: Trans. Am. Gynec. Soc. 24: 511, 1899. (2) Obituary: J. A. M. A. 30: 333, 1898. (3) *Pinckel, F.*: The Necessity of the Union of Obstetrics and Gynecology as Branches of Medical Instruction, Trans. Am. Gynec. Soc. 18: 18, 1893. (4) *Parvin, T.*: Trans. Am. Gynec. Soc. 18: 3, 1893. (5) *Idem*: The College and Clinical Record, December, 1888. (6) Obituary: Am. J. Obst. 37: 325, 1898. (7) Obituary: Med. Rec. New York 53: 201, 1898. (8) Obituary: New York M. J. 67: 193, 1898. (9) *Parvin, T.*: Lectures on Obstetric Nursing, Philadelphia, 1889, Lea Bros. & Co. (10) *Idem*: Address on Obstetrics, Trans. Internat. Med. Congress of Philadelphia, 1876 and 1877. (11) *Mosher, G. C.*: AM. J. OBST. & GYNEC. 13: 419, 1927. (12) *Parvin, T.*: The Science and Art of Obstetrics, Philadelphia, 1886, Lea Bros. & Co. (13) *Mosher, G. C.*: Surg., Gynec. & Obst. 47: 569, 1928.

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Lissimore and Currie: Studies in Vaginal Fluid, J. Obst. & Gynec. Brit. Emp. 46: 673, 1939.

A series of 105 cases of vaginal discharge was examined. The majority of patients (66.9 per cent) were the hosts of *Trichomonas vaginalis*. This organism in the opinion of the authors is not pyogenic but is associated with a lowering of the normally high acidity of the vaginal contents, and thus with removal of one of the most powerful barriers to infection by pyogenic invaders, of which the *Staphylococcus pyogenes aureus* is by far the commonest in their series. This accounts for the frequent association of the flagellate with pus, secondary infection being more usually present. There are two possible explanations of this association of the flagellate with decreased acidity:

A. The trichomonas is antagonistic to the bacillus of Döderlein. It also impedes the normal desquamation of vaginal epithelium. Thus both factors, closely associated with normal vaginal acidity, are reduced or absent.

B. The acidity of the vagina suffers great antecedent reduction by at least two natural factors, namely (1) the presence of menstrual lochia during periods, and (2) the deposition of semen during intercourse. The trichomonas, finding once again a medium of a pH agreeable to its existence, readily reestablishes itself. It is thus not necessary to postulate direct infection from the male during intercourse. Either of these two factors would explain the reappearance of trichomonas after apparent cure.

In the 33.1 per cent of cases in which trichomonas is absent, pyogenic infection explains the qualitative abnormalities of the vaginal fluid, and, as in the trichomonas positive cases, the *Staphylococcus pyogenes aureus* appears to be the commonest invader.

J. P. GREENHILL.

of all live births in the United States occurred in hospitals, but 81 per cent of all live births in cities occurred in hospitals, as compared with 22 per cent of live births in rural areas. Of all white infants, 55 per cent were born in hospitals, as compared with 23 per cent of the negro infants.

The proportion of births in hospitals has increased considerably during the period of record. In 1935, 37 per cent of the live births occurred in hospitals, as compared with 51 per cent in 1939.

#### SUMMARY

The reduction in the maternal mortality rate attained in 1939 and in each of the five years of Federal and State cooperation under the Social Security Act is well marked. The lives of 11,000 mothers have been saved during the period 1935 to 1939 that would have been lost had the maternal mortality rate of 1934 prevailed through these years; and the lives of 800 mothers were saved in 1939 that would have been lost had the mortality rate been as high in that year as in 1938. If the maternal mortality rate of 24 already achieved by 3 states had been applicable to the entire United States in 1939, there would have been only 5,437 deaths instead of 9,151.

A concentrated effort should be made to extend and improve medical and hospital services in the states with the highest mortality. A maternal mortality rate of less than 20 per 10,000 live births now seems possible of attainment. This rate will, however, be attained for the country as a whole only when every maternity patient seeks and can obtain competent medical care throughout the maternity cycle and, when needed, care in a hospital with an approved maternity service.

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Fleck, Stephen, Snedeker, Elizabeth F., and Rock, John: *The Contraceptive Safe Period*, New England J. Med. 223: 1005, 1940.

A detailed analysis is presented of observations and results as recorded by the Rhythm Clinic of the Free Hospital for Women in Brookline, Mass., covering a period of not quite four years.

A few important data only can be quoted from this elaborate report.

"The fertile period extends from and including nineteenth day before the *earliest* likely menstruation up to and including the ninth day before the *latest* likely menstruation. In each case the apprehended dates of menstruation are derived from the patient's written record of previous catamenial dates."

For about 6 per cent of the women applying for advice, the method was inapplicable; at least 14 per cent of those who could use it became dissatisfied; approximately 6 per cent were incapable of observing the rules; and about 3 per cent of the patients suggested true failure of the method. The figures indicate that though the corrected failure rate among 207 patients is only 3 per cent, the method is inappropriate for about one-third of women.

Their final conclusion is that the safe-period method constitutes a workable form of contraception for a selected group of women. On the other hand, it is doubtful whether the method is reliable enough for individual cases in which contraception is an essential safeguard of the patient's health.

HUGO EHRENFEST.

Hemorrhage, trauma, and shock were responsible, in all, for 20 per cent (1,808) of the 9,151 deaths. Most (1,617) of these 1,808 deaths occurred during or after childbirth; 130 were due to hemorrhage following abortion, and 61 to hemorrhage of pregnancy.

TABLE I. MATERNAL MORTALITY, BY STATES, 1939

STATE (NUMBER OF DEATHS IN 1939)	MATERNAL MORTALITY RATE*	STATE (NUMBER OF DEATHS IN 1939)	MATERNAL MORTALITY RATE*
United States (9,151)	40	Maryland (105)	37
Idaho (24)	22	Kansas (108)	37
North Dakota (32)	24	Pennsylvania (613)	38
Oregon (40)	24	Maine (59)	39
Connecticut (60)	26	Ohio (424)	39
Wisconsin (151)	28	Oklahoma (176)	40
South Dakota (34)	29	Nevada (8)	41
Minnesota (148)	29	Delaware (18)	41
Iowa (131)	30	Missouri (243)	41
Utah (40)	31	Kentucky (262)	43
Michigan (289)	31	Arizona (48)	44
California (321)	31	North Carolina (374)	47
Illinois (370)	31	Texas (590)	49
Montana (35)	32	New Mexico (71)	50
New Jersey (182)	32	Virginia (268)	51
New York (603)	32	District of Columbia (73)	52
West Virginia (136)	33	Colorado (111)	54
New Hampshire (27)	34	Tennessee (297)	56
Rhode Island (35)	34	Georgia (362)	56
Wyoming (17)	35	Arkansas (202)	57
Nebraska (78)	35	South Carolina (253)	59
Massachusetts (224)	35	Mississippi (307)	59
Vermont (23)	36	Alabama (361)	59
Washington (95)	36	Louisiana (302)	62
Indiana (210)	36	Florida (211)	65

\*Maternal deaths per 10,000 live births.

Based on data from the Bureau of the Census.

TABLE II. MATERNAL DEATHS FROM EACH CAUSE AND TIME OF DEATH WITH RESPECT TO DELIVERY, UNITED STATES, 1939\*

CAUSE OF DEATH	TOTAL		ABORTION AND ECTOPIC GESTA- TION NO.	DURING PREG- NANCY NO.	DURING OR AFTER CHILD- BIRTH NO.
	NUMBER	PER CENT DISTRIBU- TION			
All causes	9,151	100	2,160	1,378	5,613
Infection	3,834	42	1,481	--	2,353
Toxemias of pregnancy	2,232	24	93	990	1,149
Hemorrhage, trauma, and shock	1,808	20	130	61	1,617
Other specified causes	471	5	456	--	15
Causes not stated	806	9	--	327	479

\*Based on data from the Bureau of the Census.

Physicians failed to give satisfactory information as to cause for 9 per cent (806) of the 9,151 maternal deaths. These deaths include those for which the physician stated the cause in such general terms as pregnancy, multiple pregnancy, and dead fetus in utero, or indicated little more than that a child had been born to the mother and that the birth was the most important factor in the death.

There were 2,265,588 live births registered in 1939. About one-half (1,138,185) of these births occurred in rural areas, the other half (1,127,403) in urban areas, that is, in cities of 10,000 or more population. Slightly over half (51 per cent)

obstetricians to review the situation seriously and correct our own shortcomings before those who are less competent attempt to correct them for us.

Premature deaths in New York City have been tabulated for the first twenty-four hours as well as for the first month of life (Table II). These figures show

TABLE II. MORTALITY UNDER ONE MONTH AND UNDER ONE DAY BY WEIGHT GROUPS  
NEW YORK CITY, 1939

WEIGHT GM.	TOTAL BIRTHS UN- DER 2,500 GM.	DEATHS UNDER ONE MONTH		DEATHS UNDER ONE DAY	
		NO.	MORTALITY %	NO.	MORTALITY %
Under 1,000	370	344	93.0	289	80.0
1,000 to 1,500	582	376	64.0	243	42.0
1,500 to 2,000	1,326	318	24.0	167	12.6
2,000 to 2,500	5,013	303	6.0	144	2.8
Total	7,291	1,341	18.4	851	11.6

the startling fact that 851, or over 63 per cent, of the 1,341 deaths under one month occurred on the first day. If the obstetrician believes that his responsibility ends with the birth of the child; and if the pediatrician refuses to accept responsibility for all infants who do not live over twenty-four hours, are we to conclude that these 851 infants, who comprised 63 per cent of the deaths under one month, were abandoned? Of course, they were not abandoned as individuals. The physician instinct in both the obstetrician and pediatrician made them give to each of these prematurely born infants the best of their efforts. Nevertheless, these 851 infants as a group were neglected in the sense that constructive thought has not been directed toward their welfare by the two specialties which should be jointly responsible for that welfare.

Of the 370 infants weighing under 1,000 Gm., 80 per cent died on the first day and 93 per cent within one month (Table II). Almost half of those between 1,000 and 1,500 Gm. failed to live twenty-four hours, and about two-thirds of this group survived less than one month. From these figures, it seems reasonable to conclude that the best way to prevent mortality in the groups of infants weighing under 1,500 Gm. is to prevent the conception of such infants or to delay their birth until they are large enough to withstand the hardships of extrauterine life. This conclusion is further substantiated by the fact that the largest percentage of prematurely born infants who have intracranial hemorrhage, as well as the largest percentage of surviving prematures who are mentally defective, are to be found in the infants who weigh under 1,500 Gm. at birth.<sup>1</sup>

Although some of the arguments offered in favor of contraception and sterilization are open to controversy, women who have progressive hypertensive disease, nephritis, severe diabetes, and the graver types of anemia should be sterilized or should practice contraception. In the milder anemias and other diseases due to nutritional deficiencies, as well as in syphilis and active tuberculosis, pregnancy should be avoided until the condition is cured.

Fig. 1 graphically shows the large proportion of infants who died on the first day and strikingly illustrates the marked reduction in mortality which accompanied each 500 Gm. addition in weight. From this chart, we may again conclude that the best way to lower the death rate of infants under 1,500 Gm. in weight is to prevent conception or to prolong their intrauterine life. In fact, the great reduction shown for each shift to the right directs our attention to the value of prolonging the pregnancy in each of the weight groups. In the so-called causeless cases of premature birth which, incidentally, are the most frequent of all premature deliveries, this can be accomplished, to a large extent, by more careful supervision of the hygiene of pregnancy.

#### PRENATAL CARE

Among the various items which are included in all good prenatal care routines, certain measures are of particular importance. These include early examination

# Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

## HOW CAN THE OBSTETRICIAN AID IN REDUCING THE MORTALITY OF PREMATURELY BORN INFANTS?\*

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**D**URING the year 1939, 99,700 infants of known weight were born alive in the city of New York. Of these, 7,291, or 7.3 per cent, weighed under 2,500 Gm. Since this weight level is considered a good index of prematurity, it may be stated that the incidence of prematurely born living infants in New York during that year was approximately 7.3 per cent.

Thirteen hundred and forty-one, or 18.4 per cent, of these 7,291 infants who weighed under 2,500 Gm. died during the first month of life, while only 948, or 1.2 per cent, of those above 2,500 Gm. failed to survive the same period (Table I). The

TABLE I. INFANT DEATHS UNDER ONE MONTH (NEW YORK CITY, 1939)

	TOTAL BIRTHS	TOTAL DEATHS	PER CENT
Infants of known weight	99,700	2,289	2.3
Infants under 2,500 Gm.	7,291	1,341	18.4
Infants over 2,500 Gm.	92,409	948	1.2

hazard for the premature, accordingly, was over fifteen times as great as was that for the child born at term. Although the prematurely born infants made up only 7.3 per cent of the total 99,700 live births of known weight, the prematures who died within thirty days constituted almost 60 per cent of all of the deaths under one month.

From these figures, it is evident that any appreciable lowering of the death rate in the first month of life can be accomplished only by lowering the 7.3 per cent incidence of premature deliveries or by reducing the 18.4 per cent mortality of this group.

The first of these considerations, namely, the prevention of premature interruption of pregnancy, falls entirely within the realm of obstetrics. The lowering of the 18.4 per cent mortality for the first month is a matter for joint consideration by the obstetrician and the pediatrician. The fact that the obstetrician turns a living premature infant over to the pediatrician does not absolve him from all blame, should the infant fail to survive. On the other hand, pediatricians often are reluctant to assume even their share of the responsibility. A review of the reports of various pediatric services which include the care of the newborn infant shows a growing tendency to list premature deaths into three groups: Those who fail to survive twenty-four hours; those who die within forty-eight hours; and those who are lost within one month. Behind this tendency is the intent to shift the responsibility for the first two groups back upon the obstetrician. In some instances, the pediatricians have even gone so far as to tell the obstetrician how he should deliver these individuals. When such a state of affairs is reached, it is time for us

\*Read at a meeting of the Michigan Society of Obstetricians and Gynecologists at Detroit, Michigan, December 3, 1940.



to lessen the irritability of the uterus. Violent exercise should be prohibited. This prohibition includes tennis, horseback riding, and the more strenuous sports. Moving of furniture and other exertions which necessarily accompany house cleaning and change of domicile are too strenuous for the woman who is pregnant and are quite certain to cause disaster in those who are predisposed to the interruption of gestation. The same may be said of long journeys by auto, railroad, or steamship during which the constant vibration may cause the onset of labor.

*Sexual Relations.*—Because coitus may bring on labor, abstinence from sexual relations in the last trimester is advisable. This precautionary measure is especially indicated in those women who have had a blood-stained vaginal discharge at any time during pregnancy as well as in those who have shown evidence of the predisposing causes of prematurity.

*Danger Symptoms.*—Finally, it should be the aim of prenatal care to bring the patient into touch with her physician whenever headache, edema, rapid gain in weight, or visual disturbances appear as evidences of toxemia, or whenever abdominal pain and vaginal bleeding indicate the imminence of premature labor, in order that immediate steps may be taken to prolong the pregnancy. These should include rest in bed, the administration of large doses of progesterone, and the treatment of the underlying cause of the uterine irritability. Some of the predisposing factors are sufficiently important to warrant separate consideration.

### TOXEMIA

Toxemia often is responsible for the premature interruption of pregnancy, and, in some reports, it heads the list of etiologic factors. Since careful supervision of the hygiene of pregnancy will usually prevent its occurrence, adequate prenatal care offers the best means of diminishing premature births and premature mortality from this cause.

In the presence of an uncontrollable and rapid increase in blood pressure, albuminuria and edema, continuance of the pregnancy subjects the mother to the danger of eclampsia. At the same time, there is considerable risk that the child may perish in utero. The interests of the mother and child, therefore, call for a rapid emptying of the uterus. Cesarean section, accordingly, is given preference over the ordinary methods of inducing labor. When the operation is done under local anesthesia and without preliminary sedation, an excellent maternal and fetal result is the rule. The use of sedatives prior to operation, on the other hand, increases the risk to the fetus and general anesthesia adds greatly to the hazards of mother and child.

Intermediate between the cases in which prophylactic care eliminates all cause for anxiety and those rare ones in which only radical interference prevents a catastrophe, are to be found various perplexing gradations of toxemia. If the condition cannot be relieved but does not progress, pregnancy should not be interrupted until the fetus has reached a size compatible with extrauterine existence, even though prolongation of the toxemia may lead to residual vascular damage in the mother. In all such cases, as well as in those which slowly progress in spite of treatment, the fetus in utero, as well as the mother, is entitled to the benefit of competent consultation. This consultation, together with roentgenologic estimation of the size of the fetus, should eliminate the majority of premature labors which are induced before the weight of the fetus reaches 1,500 Gm.

### CARDIAC DISEASE

Cardiac disease may also be responsible for spontaneous or artificial interruption of pregnancy before term is reached. Such interruptions usually occur during or soon after congestive failure in women who have severe heart lesions. Most of these patients begin their gestations with a cardiac reserve which is unequal to the strain of pregnancy. In the majority of them, a careful history and physical examination before conception is permitted would reveal the fact that the cardiac condition is too grave to warrant the risk of pregnancy. Proper preconceptional advice,

by the physician, routine laboratory and physical examinations throughout pregnancy, careful instructions concerning diet, coitus, rest and exercise, and emphasis on the need for immediately informing the physician whenever any untoward symptoms occur.

Incorrect conceptions regarding daily food requirements are so prevalent that careful instructions concerning the proper balancing of the diet during pregnancy are imperative. These instructions should be specific. They likewise should consider the likes and dislikes of the individual patient. In clinic practice, where the financial status of the patient makes it difficult for her to obtain the more costly foods, she should be shown how proper nourishment can be secured within her means. This may require instruction not only in the purchase of foods but in the

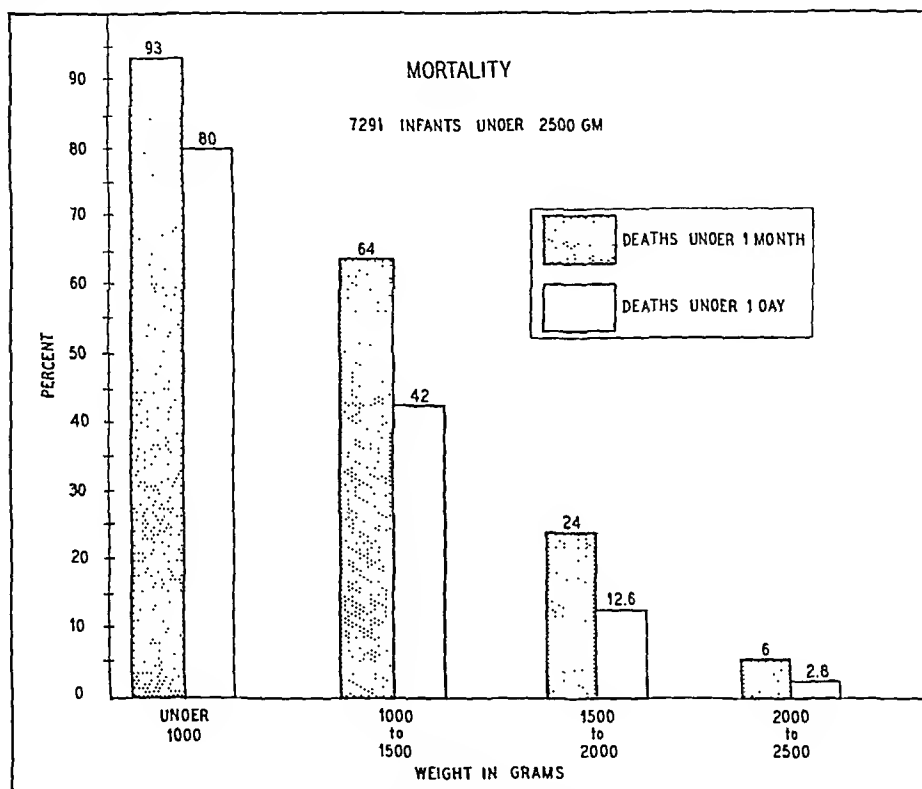


Fig. 1.—Deaths of infants under 2,500 Gm. during the year 1939 in New York City. The percentages are plotted along the perpendicular and the various weight groups along the base line. The stippled figure represents the mortality during the first month of life while the open one shows the percentage of deaths on the first day. For each addition of 500 Gm. in weight, the percentage of deaths on the first day, as well as during the first month, is greatly reduced.

make-up of menus and in the actual preparation of the less costly articles. In our Clinic, we have devised balanced diets for each month of the year at an average cost of slightly over thirty cents per day. We also are preparing a set of instructions which includes the methods of cooking which will make these inexpensive foods more palatable.

*Rest and Exercise.*—Proper advice concerning rest and exercise should aid in reducing the incidence and mortality of prematurity. Adequate sleep at night and some rest in the middle of the day are essential for all pregnant women. This is particularly important during the last half of pregnancy and is imperative in those women who have any of the conditions which predispose to premature labor. Whenever spontaneous interruption of pregnancy seems imminent, complete and prolonged rest in bed is indicated and large doses of progesterone should be given

Under proper medical management, the improvement which takes place after the eighth month when the blood volume begins to fall, is often so great that spontaneous delivery at term may be awaited and all thoughts of terminating the pregnancy dismissed.

Patients with well-compensated lesions, without a history of previous failure, seldom have difficulty and, in them, the risk to the child is approximately the same as for noncardiac cases, provided they are properly supervised. Because cardiac lesions, even when well-compensated, are treacherous complications, joint care by the cardiologist and obstetrician is most desirable.

### SYPHILIS

Although most investigators attach less importance to syphilis as a cause of prematurity than was the custom in former years, maternal syphilis still occupies a prominent place among the etiologic agents. Since it occurs four and one-half times more commonly among the colored than among the white mothers,<sup>3</sup> the control of syphilis is of particular importance in the prevention of prematurity in our colored population.

Because the usual manifestations are mild or masked in many women, and because the disease tends to be latent during pregnancy, the Wassermann reaction should be determined as a routine measure early in every pregnancy. As soon as the diagnosis is made, treatment with arsphenamine and bismuth should be commenced. Early and thorough use of these drugs will assure the birth of a living and healthy child in at least 90 per cent of the cases. The recognition and treatment of syphilis during pregnancy, accordingly, is one of the most fruitful fields for the prevention of premature birth and premature mortality.

### PLACENTA PREVIA AND PREMATURE SEPARATION OF THE PLACENTA

While placenta previa and premature separation of the normally implanted placenta are rather rare in ordinary practice, these grave complications are relatively important causes of premature birth in obstetric hospitals. Although the occurrence of placenta previa is an unavoidable complication of pregnancy, premature separation of the placenta can be prevented in many instances by preventing the occurrence of toxemia. That part of prenatal care which has to do with the prophylaxis of toxemia, therefore, may also serve as a prophylaxis against some of the premature births which are caused by separation of the normally implanted placenta. Whether the underlying pathology can be prevented or not, much can be done to diminish the infant and maternal mortality which results from these major complications, by having the patient report to her physician whenever vaginal bleeding of any kind is observed.

The growing tendency to employ cesarean section in the treatment of placenta previa and ablatio placentae should increase the chances of obtaining a living infant capable of surviving. Reports from some clinics, however, do not justify such optimism. Although the mortality of the premature infants delivered by cesarean section for placenta previa at the Boston Lying-in Hospital was considerably lower than that obtained by other methods of treatment, fully 50 per cent of the infants thus delivered were lost.<sup>4</sup> It may be possible that the use of pre-operative sedation and general anesthesia was responsible for some of these deaths. On the other hand, local anesthesia, without preliminary sedation, is used in our clinic and, in spite of this precaution, we have observed a higher mortality for premature infants delivered by abdominal section in cases of placenta previa than for those similarly delivered in other complications. It may be possible that the loss of blood by the mother produces an anoxia of the fetal brain with residual damage, from which it is unable to recover. If this is true, more frequent and larger transfusions prior to operation should help the fetus as well as the mother.

While most good obstetricians subscribe to the dictum that there is no expectant treatment for placenta previa, the great improvement in and accessibility to obstetric hospitals may lead us to modify this dogmatic rule in the interests of the premature infant. Should this rule be so changed, those cases of placenta previa

therefore, will eliminate the possibility of premature delivery and premature mortality in most instances of this character. However, many of these unfortunate women, who are under the care of their physician, either receive no advice concerning the risk of pregnancy or they disregard such advice. As a result, the seriousness of this complication is not realized until they present themselves for prenatal examination.

Congestive failure resulting from the extra load of pregnancy is not uncommon in these cases and, because of it, the pregnancy may be interrupted prematurely. In Hamilton's series of 514 cardiac patients, 53 were thus terminated.<sup>2</sup> While the infant mortality was slightly less than 4 per cent after the thirty-fifth week, over 50 per cent of the viable infants delivered prior to the thirty-sixth week were lost. Thus it may be stated that the premature infant is particularly susceptible to the effect of congestive failure in the mother, even though the more mature fetus is relatively unaffected thereby.

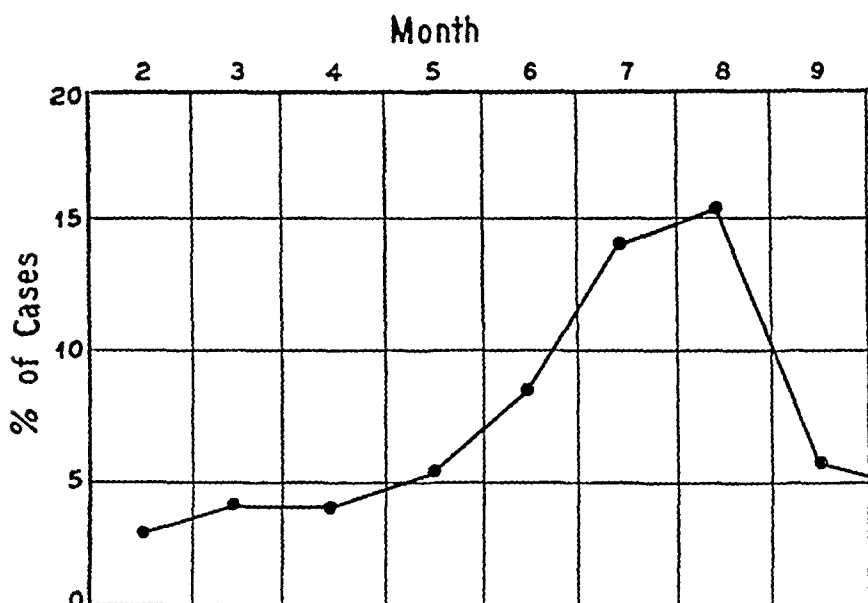


Fig. 2.—Incidence of cardiac failures in the various months of pregnancy (Carr and Hamilton). Note the precipitate fall in the number of failures after the eighth month.

Because the risk to the fetus in these cardiac cases decreases rapidly with each added month of intrauterine life, it is essential that spontaneous interruption of gestation be prevented and artificial termination be postponed as long as the best interests of the mother will permit. In this connection, it may be well to note the observations of Carr and Hamilton concerning the period of gestation in which congestive failure is most likely to occur (Fig. 2). While, according to them, congestive failure may occur at any month, the incidence of its occurrence is rather low up to the sixth month, after which it rises rapidly to reach a peak in the eighth month. Soon thereafter the tendency toward a break in compensation rapidly diminishes. These observations concerning the decrease in both maternal and fetal risk after the eighth month make imperative obstetric and cardiologic consultation in order that both mother and child may have the benefit of the optimum time for delivery.

Because the combination of prematurity and congestive failure is decidedly unfavorable for the child and because delivery or operative interference during a break in compensation is most hazardous for the mother, a pregnancy should not be terminated artificially in the course of congestive failure. By waiting until the patient has recovered from the break in compensation or until no further improvement is possible, both the mother and child will have a better chance for survival.

## PRESSURE EFFECTS

Not only are the pressure effects of labor more injurious to the premature than to the full-term infant, but the frequency and extent of the damage done vary inversely with the duration of pregnancy. In other words, the smaller the fetus, the greater will be the risk of serious injury during delivery. Most of the danger is encountered in the second stage during which pressure on the uteroplacental circulation may cause oxygen deprivation varying from mild anoxia of the brain to complete asphyxia, or, pressure of the soft and malleable head against the resisting pelvic floor may produce brain injury and intracranial hemorrhage. On account of these dangers, the membranes should be preserved as long as possible and the second stage of labor should be terminated shortly after the head reaches the level of the ischial spines. The latter usually can be accomplished by doing an episiotomy under local anesthesia. Since this procedure removes most of the resistance at the outlet, it should be done in all cases. If the birth of the head does not follow soon after the episiotomy is done, extraction by low forceps is indicated. When the blades are carefully applied and only gentle traction is made, the low forceps operation protects the child's head from injury. As a result, low forceps after episiotomy gives the lowest mortality of all methods of delivery.

## VITAMIN K

Because the brain of the premature fetus is poorly protected by the imperfectly developed intracranial supporting connective tissues and because the blood vessel walls cannot withstand as much pressure as those of the full-term infant, brain injury and intracranial hemorrhage are more common in premature than in full-term labors. If the child has a hypoprothrombinemia, the slightest injury to an intracranial vessel may cause serious bleeding. For this reason, vitamin K should be given to the mother several hours before premature termination of pregnancy is artificially attempted and every four hours during all premature labors.

## CONSERVATION OF HEAT AND AUTOTRANSFUSION

Immediately after delivery and before the cord is tied, the newborn premature infant should be placed in a tub of warm sterile water to prevent the shock which might follow a sudden chilling of the body surface and to protect it against any unnecessary heat loss while waiting for the cord to stop pulsating. Often the cord is clamped and cut at once in order that the child may be immediately placed in an incubator. This practice is reprehensible since it deprives the immature infant of considerable blood which it otherwise might take up from the placental circulation. By the use of the warm tub, the attendant not only can wait for the pulsations to cease but he can strip the cord toward the child and thus add still further to its blood volume. In addition to permitting time for this autotransfusion, the warm bath also makes it possible to aspirate retained material from the nasopharynx without chilling the child.

## RESUSCITATION

All attempts to stimulate respiration should be made with great gentleness and under no circumstances should the child be plunged alternately into cold and hot water. Because the vital centers in the brain may be suffering from the results of anoxia produced during the delivery, the various chemical respiratory stimulants may do more harm than good. Carbon dioxide and alphalobelin, accordingly, should not be used until the attendant is certain that sufficient oxygen is available to the brain cells to support their metabolic activity. If in doubt as to what to use, no harm and much good may result from the giving of oxygen.

## BREECH

If breech extraction and internal version are accompanied by considerable fetal risk when these operations are done at full term, the risk should be and is much greater when the fetus is premature and fragile. Breech extraction and internal

which are then recognized before the fetus has a good chance of surviving, will be hospitalized and treated with large doses of progesterone to diminish the irritability of the uterus, in the hope that the bleeding may be arrested and the pregnancy prolonged until a child of more than 1,500 Gm. can be obtained.

#### MULTIPLE PREGNANCY

While the fetuses tend to be smaller in plural than in single pregnancies of the same duration, the additional risks of multiple pregnancy more than offset the added intrauterine life which premature twins enjoy over single pregnancy infants of similar weight. These risks include the greater tendency toward nutritional deficiencies, toxemia, cardiac failure, overdistention of the uterus, uterine atony, malpresentation and operative delivery. In multiple pregnancies, therefore, all of the recommendations concerning the hygiene of pregnancy are doubly important.

Because of the overdistention of the uterus, precaution should be taken to prevent the onset of premature labor. Once labor is established, its management should be as conservative as possible. The second twin should not be delivered by version and extraction just because the passages have been prepared by the delivery of the first twin. If the presentation of the second fetus is longitudinal, interference should be limited to rupture of the membranes and Nature should be permitted to complete the delivery. Only after a delay of at least one hour is version justifiable, since *version and extraction is a dangerous procedure when the fetus is premature.*

#### INTERRUPTION OF PREGNANCY

One of the most promising fields for improvement in our prematurity end-results is that which is concerned with the artificial termination of pregnancy. Regardless of the method employed to bring about the emptying of the uterus, the greatest improvement will come from a more careful consideration of the size of the fetus and the period of gestation. Thoms and others have observed a definite relationship between the length of the occipitofrontal diameter and the length and weight of the fetus.<sup>4, 5</sup> By the use of roentgen rays, the length of this diameter can be measured and from it the size of the fetus estimated. Whenever possible, therefore, the length and weight of the fetus should be determined by roentgenologic examination before pregnancy is interrupted. The unborn fetus also is entitled to the benefit of consultation with another experienced obstetrician in order that the pregnancy may be prolonged until the premature child's chance for survival is good. These two measures should accomplish much in the reduction of the mortality of prematurely born infants.

#### SEDATIVES

In the management of premature labors, the use of the various sedative drugs and anesthetics has caused considerable controversy. The work of Snyder and Rosenfeld shows definitely that all of the drugs ordinarily used for the purpose of producing analgesia, amnesia and anesthesia in the mother, have a depressing effect upon the fetal respiratory movements.<sup>6</sup> Their observation would seem to indicate that the immature brain of the premature infant should not be further handicapped by the depressing action of these drugs. On the other hand, Grier and Lussky, in a series of 453 premature infants, observed that the mortality for the infants whose mothers had been given these drugs was no higher than might be expected for their respective weight groups.<sup>7</sup> Since 410 of the 453 received sedation or anesthesia or both, the similarity in the end-results of the drug cases and the end-results of the entire series is to be expected. Comparison of their figures with those of New York City, likewise, shows a higher mortality among their drug and anesthesia cases for each weight group than is recorded for similar groups in New York. Although conclusions drawn from a comparison of this kind are not infallible, they seem to substantiate the deduction which might be drawn from the work of Snyder and Rosenfeld. Until further data are available, therefore, it is reasonable to conclude that sedative drugs and general anesthetics should not be given in the course of premature labor.

## SUMMARY

1. Although only 7.3 per cent of the total living infants of known weight born in New York City in 1939 were prematurely born, the prematures who died within thirty days made up almost 60 per cent of the total deaths under one month.

2. Of the 1,341 deaths under one month, 851, or 63 per cent, occurred on the first day.

3. The best way to prevent mortality in the groups weighing under 1,500 Gm. is to prevent conception of such infants or to delay their birth until they are large enough to withstand the hardships of extrauterine life.

4. Many premature deliveries may be prevented and the interruption of pregnancy postponed by adequate prenatal care.

5. If pregnancy is interrupted by cesarean section because of a fulminating toxemia, the operation should be done under local anesthesia and without the preliminary administration of sedatives.

6. In cardiac disease, congestive failure is especially dangerous to the premature infant. It, therefore, should be prevented by joint care of the mother by a competent cardiologist and obstetrician.

7. Syphilis should be recognized by the use of routine Wassermann determinations and prematurity prevented by vigorous treatment of the mother throughout pregnancy.

8. The dictum that there is no expectant treatment for placenta previa may have to be modified in the interests of the child. Careful observation in a good hospital and the use of large doses of progesterone might save some of the premature infants who are now lost in cases of placenta previa.

9. When a second twin lies longitudinally, it should be permitted to deliver spontaneously if possible. Only after a delay of at least one hour is version and extraction of a premature infant justifiable.

10. Before artificially interrupting pregnancy, the size of the child should be estimated by means of the x-ray and consultation with another competent obstetrician always is indicated.

11. In the management of premature labor, morphine, scopolamine, the barbiturates, and general anesthesia should not be given.

12. Vitamin K should be given to the mother before premature interruption of pregnancy is attempted and throughout all premature labors.

13. The membranes should be preserved as long as possible and episiotomy should be done to protect the premature infant from the pressure effects of labor.

14. If possible, premature infants should be placed in a tub of warm water immediately after birth and allowed to remain there until the cord stops pulsating.

15. Immediate tying of the cord robs the infant of the much needed blood which it otherwise might obtain from the placenta. Blood in the umbilical cord should be stripped toward the fetus before the umbilical cord is ligated.

16. Low forceps preceded by episiotomy is a desirable method of delivery, especially if the second stage tends to be prolonged.

17. Cesarean section at times is a valuable method of delivery. It should be done under local anesthesia without preliminary sedation. The child should be delivered head first, and, if possible, the tying of the cord should be somewhat delayed in order that the fetus may obtain some of the blood which is in the placental circulation.

I wish to thank Mr. Thomas J. Duffield and Dr. Sylvia L. Parker of the Bureau of Records for their kindness in furnishing me with the statistics on premature mortality in New York City.

## REFERENCES

- (1) *Brander, T.*: Studien über die Entwicklung der Intelligenz bei Frühgeborenen Kinder, Helsingfors and Berlin, 1936. (2) *Teel, H. M.*: AM. J. OBST. & GYNEC. 30: 53, 1935. (3) *Peckham, C. H.*: J. Pediat. 13: 474, 1938. (4) *Clifford, S. H.*: J. Pediat. 5: 139, 1934. (5) *Thoms, H.*: AM. J. OBST. & GYNEC. 20: 807, 1930; 29: 876, 1935. (6) *Snyder, F. F., and Rosenfeld, M.*: Am. J. Physiol. 119: 153, 1937. (7) *Grier, R. M., and Lussky, H. O.*: AM. J. OBST. & GYNEC. 39: 669, 1940.

version, therefore, are the most dangerous of all obstetrical operations when the child is premature and should not be done if they can be avoided. In breech presentation, external version before or at the onset of labor often can be accomplished, and the need for breech extraction at times may thus be eliminated.

#### CESAREAN SECTION

Cesarean section should be the safest method of delivering a premature infant. Most reports of premature end-results, on the contrary, show mortality figures much higher than might be expected. Of the 286 premature infants delivered alive by cesarean section in New York, 80, or 28 per cent, died within one month. These figures certainly do not favor suprapubic delivery. Even when considered from the standpoint of the various weight groups, the results are disappointing, as 13 per cent of the infants between 2,000 and 2,500 Gm. and 40 per cent of those between 1,500 and 2,000 Gm. failed to survive the first month (Table IV).

TABLE IV. PREMATURE MORTALITY, NEW YORK CITY, 286 CESAREAN SECTIONS

WT. IN GM.	NUMBER	DEATHS	MORTALITY %	MORTALITY FOR ALL PREMATURES %
Under 1,000	13	11	87	93
1,000-1,500	25	19	83	64
1,500-2,000	65	26	40	24
2,000-2,500	183	24	13	6
Total	286	80	28	18

When consideration is given to the fact that many of the sections were done for the worst cases of placenta previa and premature separation of the placenta, as well as in cardiac patients who had congestive failure, it may be stated that this method of delivery often was selected because of some grave maternal complication and that the fetal mortality frequently was due to the effect of that maternal complication rather than to the operation itself. We, accordingly, might take refuge behind this seemingly good explanation for our poor cesarean section results. On the other hand, might it not be well for us to review our own experience with a view to finding some constructive criticism which might better these results? In the light of my experience, the following suggestions seem warranted:

1. Cesarean section should be done only after consultation and roentgenologic examination indicate that the child is over 1,500 Gm. in weight, unless the life of the mother might be jeopardized by postponing the interruption of pregnancy.

2. Even after the fetus has reached the 1,500 Gm. limit, it is well to postpone operation if the condition of the mother and child will permit further delay.

3. Several hours before operation, vitamin K should be given to the mother as an aid in the prevention of hemorrhage.

4. No sedative drug should be given to the mother prior to operation.

5. The operation should be done under local anesthesia.

6. The low technique is preferable from the standpoint of both mother and child.

7. The child should not be grasped by the feet and violently jerked out of the uterus. On the contrary, it should be delivered head first by as gentle manipulations as circumstances will permit.

8. If there is no bleeding from the placental site and usually there is none when the low technique is followed, the cord should not be severed immediately. While waiting for its circulation to take up some of the placental blood, the child may be held by the feet so that whatever material is in the nasopharynx may drain away.

9. Vigorous methods of resuscitation should be avoided. When in doubt concerning the use of drugs, give oxygen rather than carbon dioxide and respiratory stimulants.

10. A tub of warm water or a warm crib should be at hand to prevent any unnecessary loss of heat while the infant is being transferred to its permanent quarters in the nursery.



# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Gynecologic Operations

Baistrocchi, J. D.: *The Transverse Incision in Gynecology*, *Semana méd.* 47: 1079, 1940.

The author extols the virtues of transverse incision for performing gynecologic laparotomies. He describes and illustrates the incision he uses. This type of incision should be used in all pelvic laparotomies except for the removal of very large tumors and for the performance of Wertheim operations. This incision is a definite safeguard against postoperative hernias. If drainage is necessary, it can readily be accomplished through the transverse incision, and the subsequent results are better than after drainage in longitudinal incisions.

J. P. GREENHILL.

Long, W., and Poole, W. B.: *Review of One Thousand Consecutive Hysterectomies*, *South. M. J.* 33: 1015, 1940.

One thousand consecutive hysterectomies were performed by 49 attending surgeons in a general hospital during a four-and-one-half-year period with only 9 deaths and a mortality rate of 0.9 per cent. Four deaths occurred in 785 of the operations performed by 12 of the surgeons; there were but two fatalities (0.39 per cent) in 513 operations of this series done by 5 operators. Peritonitis accounted for 4 of the deaths; 3 resulted from pulmonary embolus, and 2 from operative shock.

The supravaginal procedures numbered 923, and accounted for 8 of the deaths. In 125 of these patients the cervix was either cauterized or amputated. Fifty-seven complete abdominal hysterectomies were performed without any mortality, and 20 vaginal operations with one death. Thus the cervix was either treated or removed in 202 patients. The cervical stump, although normal in appearance, should be examined periodically.

Operative risk is increased by the performance of multiple procedures. This factor may have been responsible for some of the complications and fatalities.

Total complications numbered 122, of which there were 47 urinary tract infections. There were 25 wound infections, an incidence of 2.5 per cent. In the last 500 cases, approximately 50 per cent of the patients had a temperature elevation for more than four days. Forty patients received transfusions preoperatively, and 8 after operation.

Hysterectomy is preferable to radium therapy in women under 41 years of age, since ovarian function may be preserved.

ARNOLD GOLDBERGER.

Cooke, W. R.: *The Management of Salpingitis*, *South. Surgeon* 8: 488, 1939.

The intelligent management of salpingitis is based upon a knowledge of regional anatomy, the pathology and sequelae of such infection, the defense mechanisms of the pelvic peritoneum and internal genitalia, and the type of bacteria involved. The principles upon which are based the management of suppurative infection in the general peritoneal cavity cannot be applied to the treatment of infections in the adnexa, and pelvic peritoneum. Gonococcal infection of the tube stimulates a defense mechanism which is effectively bacteriostatic and favors complete local recovery

# Society Transactions

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## NEW YORK OBSTETRICAL SOCIETY

MEETING OF MARCH 11, 1941

The following papers were presented:

**The Occipito-Posterior.** Dr. D. Anthony D'Esopo (by invitation).

**The Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus.** Dr. G. N. Papanicolaou (by invitation) and Dr. Herbert F. Trant. (For original article, see page 193.)

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## BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF MARCH 7, 1941

The following papers were presented:

**Theca Cell Tumors of the Ovary.** Drs. Samuel A. Wolfe and Irwin Neigus (by invitation). (For original article, see page 218.)

**Remarks on Spinal Anesthesia in Obstetrics.** Dr. Samuel Cosgrove, Jersey City, N. J. (by invitation).

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## OBSTETRICAL SOCIETY OF BOSTON

MEETING OF MARCH 18, 1941

The following papers were presented:

**Prophylactic External Cephalic Version.** Dr. John L. Newell. (For original article, see page 256.)

**Clinical Correlations of X-ray Pelvimetry by Thoms' Method.** Dr. Robert H. Barker.

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## JOINT MEETING OF THE ST. LOUIS GYNECOLOGICAL SOCIETY, KANSAS CITY OBSTETRICAL AND GYNECO- LOGICAL SOCIETY, AND CHICAGO GYNECOLOGICAL SOCIETY

FEBRUARY 15, 1941, AT ST. LOUIS, MO.

The following papers were presented:

**A Study of the Ovaries and Endometriums of Patients With Fundal Carcinomas.** Drs. Harold O. Jones and John I. Brewer. (For original article, see page 207.)

**Chronic Cervicitis.** Dr. George F. Pendleton, Kansas City, Mo.

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## ST. LOUIS GYNECOLOGICAL SOCIETY

MEETING OF APRIL 10, 1941

The following papers were presented:

**Pregnancy at Term Complicated by Old Poliomyelitis With Residual Paralysis and Scoliosis.** (Motion Picture.) Dr. Paul Fletcher.

**A Report of a Case of Amenorrhea and Sterility Treated With Progesterone.** Dr. Willard M. Allen.

Genital tuberculosis is rare. Radical operative procedures are indicated; usually, it is unwise to preserve an ovary in the face of a tuberculous infection.

Today, most gynecologists recognize the relationship of violin-string adhesions over the liver to genital gonorrhea.

If one removes both Fallopian tubes, the corpus of the uterus also should be removed. If one ovary is diseased and the other one is normal, the diseased ovary should be removed in toto.

WILLIAM C. HENSKE.

Chalier, Andre: The Condition of the Adnexa in Uterine Fibroids and Their Surgical Sequelae, *Presse méd.* 47: 1221, 1939.

In the effort to determine the frequency and nature of associated adnexal disease, the author reviewed 600 cases which had been treated for uterine fibroids. He found 212 records containing a complete description of the adnexa.

In the therapeutic management of uterine fibroids, two main principles must constantly be borne in mind: first, the attendant risk of the selected procedure, and second, the possibility of maintaining physiologic function in the postoperative period.

In the 212 analyzed cases, the adnexa were recorded as normal in only 51 instances; while in approximately 75 per cent, they were in a pathologic condition. He divides the associated adnexal diseases into 3 groups: processes involving one or both ovaries, affecting one or both Fallopian tubes, and last, those involving both the tubes and ovaries.

The adnexal disease was limited to one or both ovaries in 104 cases (circa 50 per cent). This included atrophy of the ovary in 14 cases, larger ovarian lesions, seldom over orange size, in 17 and microcystic or poly- or sclerocystic ovaries in 73 cases, these latter being bilateral 46 times (21.69 per cent).

Tubal disease, in 11 cases included bilateral pyosalpinx (3), bilateral hydrohematosalpinx (5), bilateral hydrosalpinx (2), and bilateral tuberculous salpingitis (1).

Mixed tuboovarian conditions, present in 45 cases (21.2 per cent) included perimetritis of prolapsed adnexa (3 cases) and true adnexitis (32 cases).

In these 161 instances of associated adnexal pathology, there were 69 cases of serious tubal, ovarian, or tuboovarian disease while in the other 73 cases the pathologic changes were of minor importance.

The 212 requiring uterine operations included 150 supravaginal hysterectomies and 38 total hysterectomies. In 24 cases more conservative surgery could be done: 6 subisthmal hysterectomies, 3 defundations, and 15 myomectomies.

Salvage of ovarian tissue during the concomitant adnexal surgery was possible in 98 instances, in 74 cases by conservation of ovarian tissue *in situ*, and in the remaining 24 operations by complete or partial ovarian grafts into the labia majora.

The author in conclusion stresses the advantage of conservatism by leaving some ovarian tissue *in situ*. He does not favor ovarian grafts. He had but one case in which preserved adnexa required operative reintervention, an ovarian infarction following removal of a uterine fibroid.

CLAIR E. FOLSOME.

Wharton, Lawrence R.: Further Experiences in the Construction of the Vagina, *Ann. Surg.* 111: 1010, 1940.

The author reports on 12 cases of constructing a vagina according to his suggested technique. The operation consists chiefly in the blunt dissection of the rectovesical space. Into this space is fitted a form of light but fairly rigid material which will not adhere to the raw vaginal walls. The author used a mold of Balsa wood covered with a rubber condom. The operation was performed by 7 different operators. The results were perfect in 8 cases, unknown in 1 case, and complete or partial failure in 3 cases. Sexual life was normal and orgasm was definitely experienced by some of the women. The vaginal mold should be sufficiently rigid to resist the constant pressure of the perineal muscles, it should be smooth, clean, sterilizable, nonabsorbent, and light so that it will not press against the rectum. The

without loss of function, providing that there is immediate and absolute bed rest. Local therapy and physical activity interfere with this reaction. The active phase of tubal inflammation subsides within seventy-two hours if bed rest is enforced at the earliest indication of salpingitis. Little damage is caused by unmixed gonococcal infection, and there is usually anatomic and functional recovery. Re-infections are usually accompanied by other organisms, and since these are in most instances of low virulence, the inherent defense mechanism continues to function, and the clinical course remains the same. Dominance of the secondary infecting bacteria is indicated by progressively active inflammation.

Gonococci tend to retain their virulence in the cervix for long periods and thus favor opportunities for autoinfection.

Diathermy, foreign protein therapy and Elliott treatment have not been of very great value in the treatment of acute gonorrheal salpingitis. Sulfanilamide may eradicate the source of re-infection in both the man and the woman; little effect can be expected upon most of the mixed infections. Operative treatment is never indicated in the active phase of infection, for at this time it is associated with a high postoperative mortality. The knowledge that regression of the infection may be followed by functional and anatomic restitution to normal with even the possibility of pregnancy should encourage the observance of a conservative regime.

Laparotomy is not performed until there has been an absence of temperature elevation above 99° F. for seventy-two hours following absolute confinement to bed, and unless the temperature does not rise following a vigorous pelvic examination at the end of this period. If the temperature fails to subside after the seventy-two-hour period of complete rest a daily examination should be made for collections of pus. These should be drained if detected.

ARNOLD GOLDBERGER.

Gardner, George H.: *The Management of Chronic Pelvic Infections*, Surg., Gynec. & Obst. 70: 370, 1940.

Although pelvic infections still occupy an extremely important position among gynecologic problems, tubal disease is a less frequent indication for surgery nowadays.

Acute salpingitis should not be a surgical problem because the disease is usually self-limited. The period of morbidity is shorter with conservative management; furthermore, acutely inflamed structures are more likely to rehabilitate themselves if they are not mutilated by operative trauma.

If one is conservative, he will find that many pelvic masses resolve promptly and spontaneously without resorting to cul-de-sac drainage.

If the tubal involvement is a simple catarrhal inflammation and the fimbriae are free, one should not remove the tubes. If the tubes are thickened, filled with pus, and the fimbriae are sealed, they may be removed.

In pelvic surgery, drains through the posterior vaginal fornix are preferable to drains through the abdominal wall. The routine use of drains after a total hysterectomy probably increases postoperative morbidity.

Sulfanilamide has found one of its chief fields of usefulness in the treatment of acute gonorrhea and in the management of postabortive and puerperal infections. Enthusiasm has been shown about pelvic heat therapy as an aid in hastening resolution of subacutely inflamed pelvic structures.

Relatively few women with acute gonorrheal salpingitis, postabortive infections, and puerperal sepsis ultimately require surgery for the correction of the residues of the acute inflammation.

One should wait at least a year, or preferably a year and one-half, after an acute attack of gonorrheal salpingitis has subsided before operating, the only exception being the individual who repeatedly is reinfected. Under such circumstances the operation should be performed soon after an acute attack has subsided, before she has an opportunity to become infected again. After a cellulitis type of infection one should postpone operation indefinitely. The presence of fever is a contraindication to surgical interference, unless one is operating to drain an abscess or to remove it. Exquisite pelvic tenderness, induration of tissues, and the presence of cellulitis usually denote a relatively active infection.

Unless the cystocele is very marked, there is no reason for the use of a retention catheter, however, if one is used it should be of plain soft rubber and must be introduced carefully and removed after five to seven days with exceeding care. In exceptional cases with little cystocele when no perineorrhaphy is done the patient may be up in a chair after two or three days and up and about in a few days more.

J. P. GREENHILL.

Pilcher, Frederick Jr., and Aikenhead, A. E.: Accidental Bilateral Ligation of the Ureters, *Canad. M. A. J.* 43: 436, 1940.

The authors report a case of accidental bilateral ligation of the ureters during the course of a total hysterectomy. Treatment consisted of bilateral nephrostomy. Four weeks later one ureter had become patent to a ureteral catheter and shortly thereafter the nephrostomy tube on the opposite side dropped out. Intravenous pyelography ten months postoperatively demonstrated normal kidney pelves, calyces, and ureters.

From a review of the literature the authors believe that the best treatment for such accidents is immediate nephrostomy rather than attempts at deligation. This should be followed later by appropriate treatment for the obstructing lesion such as end-to-end anastomosis or implantation of the ureter into the bladder or rectum. In many instances of simple ligation the lumen may be restored spontaneously.

CARL P. HUBER.

Knott, W.: The Prevention of Postoperative Thrombosis and Embolism by Means of Elevation of the Lower Extremities, *Zentralbl. f. Gynäk.* 62: 679, 1939.

Two series of obstetric-gynecologic operative cases (630 and 670 cases, respectively) were treated by similar methods for the prevention of thrombosis and embolism except that the latter group were kept for ten days with the lower extremities elevated. All patients were given a drug, "Sympatol," for a few days before operation and for fourteen days thereafter. Patients over fifty years of age and those upon whom plastic operations had been done were out of bed for short periods daily, beginning with the day of operation or the next day. Leeches were applied to the thighs on the day following operation. Except for the elevation of the foot of the bed, all patients were similarly treated. With this procedure deaths from embolism fell from 6 to 4, embolism from 20 to 5 and phlebitis from 4 to 1. Thrombosis increased from 10 to 13 cases. Details of the cases are given. The author suggests that the results warrant further investigation.

J. L. McKELVEY.

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## Items

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### American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 3, 1942, at 2:00 P.M. Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

Applications for admission to Group B, Part I examinations must be on file in the Secretary's Office not later than October 6, 1941. Applications for Group A must be in the Secretary's Office by March 1, 1942.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Atlantic City, N. J., immediately prior to the 1942 meeting of the American Medical Association.

additional use of mucous membrane grafts is not of much value, although a few pinch grafts over the end of the vaginal form have been used. Bleeding was the chief complication of this operation.

Postoperative care is important and consists chiefly of keeping the vesicorectal space clean. It may be irrigated with salt solution or boric acid. A weak antiseptic solution, such as 2 per cent mercurochrome, may be used to paint the walls of this space. The lubricated form must be worn most of the time for two months. intercourse is prohibited until the epithelium is thick and strong. The author lists two chief causes for failure. The first is due to failure to wear the vaginal form and the second to injury to the bladder or rectum that sometimes occurs in the course of the dissection.

WILLIAM BERMAN.

Grossmann, Hans: The Production of an Artificial Vagina by the Formation of Broad Based Skin Flaps, *Zentralbl. f. Gynäk.* 63: 1810, 1939.

Some of the various operations for the formation of artificial vagina are listed. The author objects to the fact that most are unduly complicated. He describes a simple method which has been satisfactory in his hands in three cases. Broad based flaps of skin are made on each side and posteriorly. The former include the labia minora and majora which are adjacent. The usual dissection is followed by the apposition of these flaps and the usual postoperative care. This skin is said to be sufficiently loose and mobile to produce long flaps. The case described in detail ended up with a vagina 10 cm. long which admitted two fingers.

The ultimate character of the vagina and the fate of accessory skin structures is not described. Indications are not discussed. Three illustrations describe the formation of the flaps and the results.

J. L. McKELVEY.

Matassarini: Rose Operation Repair of the Trigonal Muscle (Incontinence in the Female), *J. Kansas Med. Soc.* 61: 189, 1940.

In 90 per cent of these women a repair of the cystocele and perineum will give the desired relief but the other 10 per cent are not relieved of their dribbling, and many, though relieved of the incontinence, still have a marked dysuria.

This operation is done in the following manner: Royston and Rose use twilight sleep and local anesthesia of  $\frac{1}{4}$  per cent novocaine with 4 min. 1:1000 adrenalin per ounce, as they believe it facilitates the dissection of the tissues and gives better hemostasis. It may be done, also, under a general or spinal anesthetic.

The incision is an inverted T through the anterior vaginal wall from cervix to a point 1 cm. from external meatus. The vaginal flap is dissected from the bladder, being very careful to avoid injury to the urethra. The bladder is then freed from uterus by blunt dissection. The base of the incision is now carried far enough laterally to expose the base of the broad ligaments. A No. 18 French, pezzar catheter is inserted into the bladder. Traction on the catheter will clearly mark the site of the internal sphincter, just in front of the bulbous tip. Using 00 or 000 chromic catgut on a fine curved intestinal needle take a deep bite anteroposteriorly in the tissues close to the urethra approximately three-fourths of an inch behind the internal sphincter. Emphasis is placed on carrying the suture anteriorly to within 1 cm. of the meatus. Care must be taken not to carry this suture too far posteriorly, to obstruct the ureteral orifice which is normally 3 cm. behind the internal sphincter. This suture is not tied at present. Now, a similar suture is placed on the opposite side. If the cystocele is marked, a third similar suture should be placed in midline. These sutures will restore the normal axis of the urethra.

A deep mattress suture of the same material (Kelly stitch) is then placed to reinforce the internal sphincter and fix it around the trigonal muscle. The pezzar catheter is removed before any of these sutures are tied.

With No. 1 chromic catgut the fascia is brought together and reinforced with another row of sutures. The bases of the broad ligaments are sutured anteriorly to the cervix, thus elevating it. The redundant vaginal mucosa is trimmed away and the incision sutured with No. 1 chromic catgut. A perineal repair is usually added.

The candidate should have an adequate working knowledge of gross and microscopic obstetric and gynecologic pathology. If the three years are spent in one hospital or institution, organized instruction in pathology or other basic sciences should be provided. If the graduate obtains his complete training in several hospitals it would be extremely difficult for him to obtain sufficient instruction in pathology unless the various hospitals offering residencies of a year or more should arrange for such instruction. It is desirable for the trainee to have three months' full-time service in pathology or a specified number of hours weekly combined with another service for an equivalent period of time.

Candidates for the certificate of the American Board of Obstetrics and Gynecology may be eligible for examination by the Board whose graduate training was obtained under the preceptorship of a competent obstetrician and gynecologist and not necessarily as a resident or fellow in a hospital or graduate institution.

The lists of hospitals approved for graduate training in obstetrics and gynecology are published from time to time in the Educational Number of *The Journal of the American Medical Association*.

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## Books Received

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**THE THERAPEUTICS OF INTERNAL DISEASES.** Volume III. Supervising Editor George Blumer, Clinical Professor of Medicine, Yale University School of Medicine, etc., and Associate Editor Albert J. Sullivan, Adjunct Clinical Professor of Medicine, George Washington and Georgetown Medical Schools, etc. 1941, New York, D. Appleton-Century Company, Inc.

**DIE GYNAEKOLOGISCHEN OPERATIONEN.** Von Professor Dr. Heinrich Martius, Direktor der Universitaets-Frauenklinik in Goettingen. Zweite verbesserte Auflage, 424 Seiten, mit 427, zum groessten Teil farbigen Abbildungen und Bilderreihen von Kaethe Droysen. 1941, Leipzig, Verlag von Georg Thieme.

**FEMALE SEX HORMONES.** By Edward A. Doisy, Philip E. Smith, Robert T. Frank, and Elmer L. Sevringhaus. 58 pages. 1941, Philadelphia, University of Pennsylvania Press.

**SPERMATOOZOA AND STERILITY.** By Abner I. Weisman, M.D., Adjunct Gynecologist, Jewish Memorial Hospital, N. Y., etc. With a Foreword by Robert L. Dickinson. 314 pages, 77 illustrations. 1941, New York, Paul B. Hoeber, Inc.

**YOU CAN BE HAPPILY MARRIED.** By Gilbert Applehof, Jr., Rector of St. John's Church, Alma, Mich. 218 pages. 1941, New York, The Macmillan Company.

**THE DOCTOR TAKES A HOLIDAY.** By Mary McKibbin-Harper, M.D. Illustrated, 349 pages. The Torch Press, Cedar Rapids, Iowa, 1941.

**HANDBOOK OF ANAESTHETICS.** Revised by R. J. Minnitt, M.D., Lecturer in Anaesthesia, University of Liverpool, etc. With chapters on local and spinal anaesthesia by W. Quarry Wood, M.D., Surgeon, Edinburgh Royal Infirmary. Fifth edition, 103 illustrations, 364 pages. 1940, Baltimore, Williams and Wilkins Company.

**MALIGNANT DISEASE AND ITS TREATMENT BY RADIUM.** By Stanford Cade, F.R.C.S., Surgeon, Westminster Hospital, etc. 1280 pages, 623 illustrations, many in color. 1940, Baltimore, Williams and Wilkins Company.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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### Graduate Training in Obstetrics and Gynecology

The following is an excerpt from the report of the Committee on Graduate Study of the American Board of Obstetrics and Gynecology, presented at its recent meeting, May 27, 1941, at Cleveland, Ohio:

The Graduate Committee of the Board has kept in contact during the year with the Council on Medical Education and Hospitals of the A. M. A. The Council has sent the Committee a number of application blanks from hospitals requesting the approval of the A. M. A. and of the American Board on residencies in obstetrics and gynecology. The blanks which are used in these reports were arranged last year by the A. M. A. and the Graduate Committee and were presented to the Board at its annual meeting in Atlantic City.

It was decided that the recommendations of the Committee to the A. M. A. would be on the following basis: full approval, which is unqualified approval; provisional approval, which would require review of the situation within a year; action deferred, in which, in the opinion of the Committee, the conditions for approval or provisional approval have not been met, but which may be considered again within a year or two; nonapproval.

Hospitals requesting approval of residencies are allocated according to the recommendations of the Committee.

In addition the Council on Medical Education and Hospitals sent to the Committee for consideration similar blanks filled out by hospitals which had been approved previously by the Council on Medical Education and Hospitals and our Committee's action on these hospitals is enclosed.

A brief draft of the minimum requirements for residencies in obstetrics and/or obstetrics and gynecology was drawn up. In so far as possible such suggestions as have been agreed upon by the Committee have been incorporated in this draft which is herewith submitted for the discussion of the Board.

#### MINIMUM REQUIREMENTS FOR RESIDENCIES IN OBSTETRICS AND/OR GYNECOLOGY

In addition to the items on the combined report blank of the Council on Medical Education and Hospitals of the A. M. A. and the American Board of Obstetrics and Gynecology, the candidate should have the following training or its equivalent:

At least one year of hospital internship, preferably rotating, which should include service in a well-organized department of obstetrics and/or gynecology.

Following this the candidate should have the equivalent of three years' training in obstetrics and/or gynecology, preferably both, under the supervision of competent obstetricians and gynecologists, some of whom, at least, should hold the certificates of the American Board.

During the three years he should have clinical work in obstetrics and/or gynecology to include prepartum clinics and gynecologic diagnosis; out-patient obstetrics, ambulatory gynecology and minor gynecologic operations are desirable; obstetric hospital service consisting of assisting in and delivery of normal and complicated labors; gynecologic hospital service which should consist of both non-operative and operative services.

To be approved for residency a hospital should have at least 350 obstetric deliveries and an equal number of cases of gynecologic cases yearly; in such a limited service there should be at least 100 "free" deliveries. Three or more years of graduate training need not necessarily be spent in one hospital or institution.



Neuropsychiatrists have long been responsible for the care of individuals handicapped by birth injuries. Failure of efforts to relieve entirely these conditions has directed attention to their prevention. As a result, we now find some neuropsychiatrists intensely interested in obstetric methods and attempting to influence obstetricians in the choice and dosage of drugs and anesthetics used for relief of pain during labor and delivery.

In addition to all this, public health agencies have recently taken a more active interest in maternal welfare. Obstetricians are attempting to comply with the demands of many new public health rules and regulations designed to protect the lives and health of women and their newborn infants.

In other words, obstetricians now find themselves in the position of attempting to satisfy the increasing demands of an enlightened public, specialists in related fields of medical practice and their own local Departments of Health. It is probably fair to state that in no other type of specialty practice has there been manifest, on the part of individuals or health agencies, as much interest in the suitability of methods employed or the results obtained. This may be regarded as a logical development because in the practice of obstetrics a large group of essentially healthy individuals must be subjected to conditions which often involve serious risk to their lives and health.

Obstetricians can hardly fail to be conscious of this increasing demand for perfection in the results of their work. Its effect is a wholesome one in that it is an important factor in forcing us to improve hospital obstetric facilities, to develop new and better methods and to reconsider the logic of certain accepted obstetric procedures.

Interest in this subject led to a recent study of all fetal deaths occurring on the obstetric service at the Woman's Hospital during a five-year period from 1935 to 1939 inclusive. A detailed analysis was made of the causes of these deaths in relation to the health of the mothers during pregnancy, the character and management of their labors and deliveries, and the progress of infants that were born alive but died within one month after birth. The study included all deaths of viable infants born on both our ward and private obstetric services.

This study was undertaken with the purpose of placing emphasis on the more common causes of fetal deaths. It was hoped that by arousing interest in factors which had contributed to failures, management of certain obstetric complications might be improved.

In accordance with the standard of viability which we have used for a number of years, babies were considered nonviable and were excluded from this study, if they weighed less than 1,500 Gm. at birth or were less than 35 cm. in length.

Within the five-year period, 7,661 viable babies were born. Of these, 271 were either born dead or died within one month after birth. The incidence of fetal deaths was therefore 3.5 per cent, or 35 per 1,000 viable births.

In the following 15 tables (Tables I to XV), data resulting from the study of this small series of fetal deaths is summarized.

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## Original Communications

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### OBSTETRIC RESPONSIBILITY FOR THE PREVENTION OF FETAL DEATHS\*

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*(From the Clinic of the Woman's Hospital)*

WITHIN less than a decade, "maternal welfare" has become an increasingly important phase of public health. Through a better organized nationwide program of education, prospective parents are becoming aware of the advantages of modern obstetric methods. The medical profession and hospital authorities are making determined efforts to provide proper facilities to meet the growing demand for obstetric care in hospitals.

Pediatricians, responsible now for the care of newborn infants in many hospitals, have established simplified routines of infant feeding which satisfy the demands of most babies. Feeding problems in mature infants have been reduced to a minimum. As a result, pediatricians are concentrating their attention upon other problems such as development of a satisfactory routine for the care and feeding of premature infants, prevention and treatment of infections in the newborn, and measures necessary to improve the health and development of babies at birth.

Internists have become much interested in the progress of pregnancy and its effect on the health of women who are the victims of chronic organic diseases and especially those of the cardiovascular system and the kidneys.

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\*Presented at a meeting of the Washington Gynecological Society, March 15, 1941.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

In New York a large committee of pediatricians and obstetricians appointed by the Commissioner of Health is studying methods for prevention of newborn premature infant mortality. Presuming that the problem was a pediatric one, the committee was placed under the chairmanship of an enthusiastic pediatrician. After many months of collecting and analyzing statistics, the unavoidable conclusion has been reached that the problem is essentially an obstetric one.

TABLE III. DISTRIBUTION OF 271 FETAL DEATHS AS TO WEIGHT AT BIRTH AND TIME OF DEATH IN RELATION TO LABOR

TIME OF FETAL DEATH	WEIGHT AT BIRTH		TOTAL	PER CENT
	1,500 TO 2,500 GM.	2,500 GM. AND OVER		
Ante partum	25	31	56	21
Intra partum	15	61	76	28
Neonatal	60	79	139	51
Total	100	171	271	100
Per cent	37	63	100	--

It is a well-known fact that when babies are too large at time of delivery, the risk of birth injury to both mothers and their babies is increased. Table IV is a summary of the birth weights of 70 of the 271 babies in the series that were of a size recognized as above average normal when delivered.

TABLE IV. SUMMARY OF BIRTH WEIGHTS OF OVERSIZED BABIES IN SERIES OF 271 FETAL DEATHS

BIRTH WEIGHT	TIME OF DEATH			TOTAL
	ANTE PARTUM	INTRA PARTUM	POST PARTUM	
3,500 to 4,000 Gm. (7 pounds 11 ounces to 8 pounds 13 ounces)	6	20	21	47
4,000 to 4,500 Gm. (8 pounds 13 ounces to 9 pounds 15 ounces)	4	6	6	16
4,500 to 5,000 Gm. (9 pounds 15 ounces to 11 pounds 0 ounces)	2	3	1	6
5,000 Gm. (11 pounds 0 ounces)			1	1
Total	12	29	29	70

During the first month of life, prematurity and conditions associated with it, constitute by far the most important predisposing factor in the causation of infant deaths. From reliable statistics it has been estimated that the chance for survival of a baby born alive at term is more than 15 times better than that for a premature infant.

Table V is a summary of the incidence of fetal deaths in the various weight groups which occurred at the Woman's Hospital during the years 1938 to 1940, inclusive. For safety to the baby, it demonstrates the importance of prolonging intrauterine life of the fetus to as near full term as possible.

TABLE I. SUMMARY OF DATA REGARDING 271 FETAL DEATHS OCCURRING AT THE WOMAN'S HOSPITAL DURING THE YEARS 1935 TO 1939 INCLUSIVE

The study included all fetal deaths of viable babies, babies at least 35 cm. in length and weighing not less than 1,500 Gm. (3 pounds 5 ounces) at birth.

Total No. of viable births	7,661
Total No. of fetal deaths	271
Percentage of fetal deaths	3.5

Fetal death rate, 35 per 1,000 viable births.

The 271 babies were born to 269 women (2 sets twins).

HOSPITAL STATUS OF MOTHERS		BABIES WERE DELIVERED BY	
Private	116	Attending surgeons	115
Ward	155	Resident surgeons	122
		Courtesy surgeons	34
Total	271		271

TABLE II. SUMMARY OF PREVIOUS PREGNANCIES AS RECORDED IN THE HISTORIES OF 269 MOTHERS

138 Women had had no previous pregnancies.

131 Women had had 318 pregnancies which were terminated as follows:

Spontaneous abortions	42
Induced abortions	25
Premature deliveries	9
Delivery at term	242
Total	318

Outcome of the 242 babies born at term was as follows: Living babies 207; stillbirths 23; Neonatal deaths 12. The 131 mothers had lost 35, or 16.9 per cent, of babies born at term in previous pregnancies.

Since the 131 women had lost 16.9 per cent of babies born at term in previous pregnancies, it would seem reasonable to expect that an incidence of obstetric complications above average might be encountered during the pregnancies being reviewed in this study.

In the classification of newborn infants, birth weight has come to be recognized as the most reliable single index of prematurity. By this standard, babies weighing less than 2,500 Gm. (5 pounds 8 ounces) at birth are considered to be premature. In Table III, it will be noted that in the series of 271 fetal deaths to be reported, 37 per cent of the babies had birth weights ranging between 1,500 (3 pounds 5 ounces) and 2,500 Gm. (5 pounds 8 ounces) and were therefore classified as premature.

As shown in Table III, approximately one-fifth of the fetal deaths occurred in utero before the onset of labor. About one-half of the babies died either before the onset or during the course of labor. The remaining one-half were born alive but died within the first month of life.

In the past, prematurity has been considered the cause for many neonatal deaths which we now know were due to intrauterine asphyxia and birth trauma. The susceptibility of premature infants to the development of these conditions during labor and delivery is now well recognized. Because a very high percentage of neonatal deaths in premature infants are due to birth trauma and asphyxia, the responsibility of an obstetrician does not end with the delivery of a living premature infant.

Tables VII, VIII, and IX contain a detailed account of the causes for the 271 fetal deaths.

TABLE VII. SUMMARY OF CAUSES OF THE 271 FETAL DEATHS

CAUSE OF DEATH	ANTE PARTUM	INTRA PARTUM	NEONATAL	TOTAL
<b>Trauma:</b>				
Intracranial hemorrhage		2		21
Tentorial tear		8	19	9
Intracranial hemorrhage and tentorial tear		18	1	43
Hemorrhage, abdomen and intestines			25	
Hemorrhage, abdomen and lungs		1		1
Hemorrhage adrenals			1	1
Ruptured liver			2	2
Cervical dislocation			1	1
<b>Total</b>		1	49	79
<b>Intrauterine Asphyxia:</b>				
Abruptio placentae		30		12
Placenta previa	7	3	2	8
Cord around neck	1	1	6	18
Prolapsed cord	6	11	1	4
Abnormal placenta		2	2	2
<b>Total</b>	2	17	11	44
<b>Intrauterine Asphyxia and Trauma:</b>				
Congestion and edema, brain	16	1	16	18
Congestion and edema, brain and other organs		2	6	8
Cause of asphyxia?	1			
<b>Total</b>	29	16	10	55
<b>Congenital Malformations*</b>	30	19	32	81
<b>Miscellaneous*</b>	7	6	23	36
<b>Total</b>	3	4	24	31
	56	76	139	271

\*Tables VIII and IX give a detailed list of congenital malformations and miscellaneous conditions resulting in fetal deaths.

In Table VII it will be noted that 55 fetal deaths were classified as due to intrauterine asphyxia and trauma although the exact causes of these deaths were never determined. Of these 55 deaths, 29 occurred before the onset of labor and 27 of the 29 babies were macerated when delivered. Although autopsies were done on 21 of the 29 babies the exact causes of death could not be determined. One mother had eclampsia, one epilepsy, and one cardiac disease. In 26 of the 29 mothers no maternal cause could be discovered which might predispose to fetal death. Sixteen of the 29 babies were definitely premature. Sixteen intrapartum and 10 neonatal deaths of undetermined cause were also included with deaths due to trauma and intrauterine asphyxia. Autopsies were done following only 7 of these 26 deaths. Before delivery was attempted 14 of the 26 babies were either in distress or dead. A study of the circumstances which attended the labors and deliveries of these 26 babies seemed to justify definitely their inclusion among the babies that died from birth trauma and asphyxia.

In Table IX it will be noted that 11 of the 31 deaths were the result of infection and that of the 11 deaths from infections 9 were from infections of the lungs. Some of these deaths were probably due to asphyxia and intrauterine aspiration of infected amniotic fluid.

TABLE V. SUMMARY OF OUTCOME OF PREMATURE BABIES BORN AT THE WOMAN'S HOSPITAL FROM 1938 TO 1940, INCLUSIVE, IN RELATION TO BIRTH WEIGHTS

WEIGHT AT BIRTH GM.	NUMBER	DEATHS	PER CENT
1,500 to 1,750	50	14	28.0
1,750 to 2,000	58	11	18.97
2,000 to 2,250	97	12	12.37
2,250 to 2,500	166	7	4.22
Total premature births (1,500-2,500 Gm.)	371	44	11.86
Total term births (2,500 Gm. and over)	4,802	56	1.17

With improvements in the routine care of premature babies, some neonatal deaths can probably be prevented. However, the most effective means of reducing the incidence of these deaths is to reduce the incidence of premature births. This is not easy to accomplish as no cause can be found for a considerable percentage of prematurely terminated pregnancies.

In the prevention of premature fetal deaths, contraception and sterilization have a definite place. In some women with conditions such as chronic cardiovascular disease, chronic nephritis, and diabetes, which predispose to premature birth, pregnancy should be prevented. For any woman who has tuberculosis, syphilis, or subnormal physical health from any cause, pregnancy should be postponed to improve the chances for a normal pregnancy and a healthy child.

As our knowledge of the essential requirements for the health of a woman in the prenatal period increases, means may be found to reduce the incidence of premature births. Certainly women should be encouraged to follow a good routine of rest and hygiene during pregnancy with the hope of preventing premature delivery as well as other complications.

Table VI is a summary of causes of the 271 fetal deaths. Diagnosis of the cause of death was established by autopsy in 203, or 75 per cent, of the babies in the series.

TABLE VI. SUMMARY OF CAUSES OF THE 271 FETAL DEATHS

CAUSE OF DEATH	ANTE PARTUM	INTRA PARTUM	NEONATAL	TOTAL	PER CENT
Trauma		30	49	79	29
Intrauterine asphyxia	16	17	11	44	16
Asphyxia and trauma	30	19	32	81	30
Congenital malformations	7	6	23	36	13
Miscellaneous	3	4	24	31	12
Total	56	76	139	271	100
Per cent	21	28	51	100	---

75 per cent of deaths were due to trauma or asphyxia or both.

From Table VI it will be noted that trauma and asphyxia were by far the most important factors in the causation of the 271 deaths. Briefly it may be stated that trauma and asphyxia were responsible for 75 per cent of the deaths, congenital malformations for 13 per cent and miscellaneous conditions for the remaining 12 per cent.

TABLE X. CONDITION OF BABIES AT TIME OF DELIVERY IN RELATION TO BIRTH WEIGHT AND CAUSES OF FETAL MORTALITY IN THE 76 INTRAPARTUM AND 139 NEONATAL DEATHS

BIRTH WEIGHT AND CONDITION AT TIME OF DELIVERY	CAUSE OF FETAL DEATH					TOTAL	PER CENT
	TRAUMA	INTRA- UTERINE ASPHYXIA	ASPHYXIA AND TRAUMA	CON- GENITAL MALFOR- MATIONS	MISCEL.		
1,500 to 2,500 Gm.							
Normal	13	8	13	9			
In distress	6	2	5	0	9	52	69
Dead	1	3	2	2	0	15	20
Total	20	13	20	11	11	75	100
2,500 Gm. and over							
Normal	38	4	16	15			
In distress	15	3	9	1	13	86	61
Dead	6	8	6	2	3	31	22
Total	59	15	31	18	17	140	100
All babies—1,500 Gm. and over							
Normal	51	12	29	24			
In distress	21	5	14	1	22	138	64
Dead	7	11	8	4	5	46	21
Total	79	28	51	29	28	215	100

we were interested to find that in a large series of normal cases, fetal mortality was 50 per cent less after the prophylactic forceps method of delivery.

A discussion of the causes and prevention of fetal deaths would hardly be complete without consideration of modern methods of analgesia and anesthesia. Common faults in the use of these measures could be found in the records of some of the patients delivered in this series. To what extent pain-relieving drugs and anesthetics had contributed to the causes of death was not easy to determine. However, it was obvious that in some instances analgesic drugs may have been given too early in labor and that oxytocic drugs had then been employed to counteract their depressing effect on uterine contractions. In other cases rather excessive amounts of analgesic drugs had been used in divided doses at too short intervals to determine whether the preceding doses might be effective. After some inefficient labors, perhaps in part the result of too much analgesia, difficult deliveries had to be conducted too early in labor with the hope of saving babies already in distress.

It is our conviction that, for safety, administration of analgesic drugs should be postponed until labor is well established and that the dosage should be moderate, especially in premature labors. If methods for using local instead of general anesthesia can be perfected and used more extensively, danger from this source can be reduced.

It was rather astonishing to find as shown in Table X, that in the 158 intrapartum and neonatal deaths in this series from trauma and asphyxia, 66, or 41.7 per cent, of the babies were either in distress or dead before delivery was attempted. From this it may be assumed that more than four out of ten of these fetal deaths were the result

TABLE VIII. SUMMARY OF CONGENITAL MALFORMATIONS RESULTING IN 36 OF THE 271 FETAL DEATHS

DIAGNOSIS	NO.	DIAGNOSIS	NO.
Malformation of heart	4	Abnormal trachea and bronchi	3
Mongolism	2	Diaphragmatic hernia	3
Hydrocephalus	6	Atresia duodenum	1
Hydrocephalus, hypertrophic bladder and bilateral hydroureters	1	Atresia colon	1
Hydrocephalus, imperforate anus, absence of both kidneys	1	Pyloric stenosis. Malformation of chin and hand	1
Anencephalus	3	Ectopia of viscera	1
Spina bifida	1	Malformation both kidneys	1
Anencephalus and spina bifida	2	Hypoplasia adrenals	1
Anencephalus, absence of both adrenals and right kidney	1	Cleft palate, anisophthalmia	1
		Harelip, aspiration	1
		Massive umbilical hernia (eventration of viscera)	1
Total	21	Total	15

TABLE IX. SUMMARY OF MISCELLANEOUS CONDITIONS RESULTING IN 31 OF THE 271 FETAL DEATHS

CAUSES OF DEATHS	TIME OF FETAL DEATHS			
	ANTE-PARTUM	INTRA-PARTUM	NEONATAL	TOTAL
Prematurity			4	4
Postmaturity	1			1
Erythroblastosis	2		4	6
Bronchopneumonia			4	4
Bronchopneumonia and atelectasis			3	3
Bronchopneumonia and aspiration			1	1
Lobar pneumonia agranulocytosis			1	1
Icterus gravis			2	2
Anemia, icterus, splenomegaly			1	1
Edema neonatorum, parenchymatous, degeneration of internal organs			1	1
Gastroenteritis			1	1
Status thymolymphaticus		1	1	2
General peritonitis			1	1
Aspiration amniotic fluid		3		3
Total	3	4	24	31

From study of Tables VII, VIII, IX, and X, it is apparent that the best opportunity to reduce the incidence of fetal deaths is in the prevention of birth trauma and fetal asphyxia, the result of labor and delivery.

In this series of 271 fetal deaths, 215 (intrapartum 76, neonatal 139) occurred during the course of labor or within one month after birth. Of these 215 deaths, 158, or 73.4 per cent, nearly three-fourths, were due to trauma and asphyxia.

Much has been written as regards the dangers of birth injury to babies from operative interference. In the light of our present knowledge too little emphasis has been placed upon damage resulting to babies and mothers from unduly prolonged pressure of labor and the opportunity which not infrequently comes to save babies by timely and skillful operative interference.

In a study<sup>1</sup> of the comparative results of spontaneous delivery and delivery by so-called prophylactic forceps at the Woman's Hospital,





of labor rather than the delivery. Approximately 85 per cent of the 158 babies were eventually delivered by operative means.

A study of the records shows that many of these deaths occurred in unduly prolonged labors, and labors that failed to progress because of faulty positions of the presenting part, abnormal presentations and cephalopelvic disproportion that was discovered too late in labor. Timely operative interference would almost certainly have saved the lives of some of these infants.

Tables XI and XII show the methods of delivery employed in the 56 cases with antepartum death of the fetus and the 215 cases in which the fetus died during labor and delivery or in the neonatal period.

TABLE XI. METHOD OF DELIVERY EMPLOYED IN RELATION TO CAUSES OF THE 56 ANTE-PARTUM FETAL DEATHS

METHOD OF DELIVERY	CAUSE OF DEATH				TOTAL
	INTRA-UTERINE ASPHYXIA	ASPHYXIA AND TRAUMA	CON-GENITAL MALFORMATIONS	MISCEL.	
Spontaneous	7	22	6	2	37
Forceps					
Low	1				1
Prophylactic low	2	3			5
Mid	1		1	1	3
Breech					
Extraction		1			1
Version and extraction	2	1			3
Cesarean section					
Classical	1				1
Cervical	2	2			4
Vaginal hysterotomy		1			1
Total	16	30	7	3	56

TABLE XII. METHOD OF DELIVERY IN RELATION TO CAUSES OF 215 FETAL DEATHS IN 76 INTRAPARTUM AND 139 NEONATAL DEATHS

METHOD OF DELIVERY	CAUSE OF FETAL DEATHS					TOTAL	TOTAL
	TRAUMA	INTRA-UTERINE ASPHYXIA	ASPHYXIA AND TRAUMA	CON-GENITAL MALFORMATIONS	MISCEL.		
Spontaneous	10	1	13	6	8	38	38
Forceps							113
Low	11	6	7	4	6	34	
Prophylactic low	15	5	3	6	6	35	
Mid	18	5	9	5	4	41	
High	2		1			3	
Breech							35
Delivery		1	1			2	
Extraction	12	1	3	2		18	
Version and extraction	9	2	2	1	1	15	
Cesarean section							29
Classical		1	1			2	
Cervical	1	6	7	4	1	19	
Extraperitoneal	1		2		2	5	
Porro			2	1		3	
Total	79	28	51	29	28	215	215

results represented by types of cases contained in the series that has been analyzed for this report. In studying the 269 labors and deliveries which resulted in the 271 fetal deaths, it was difficult to avoid the impression that our failures were rarely due to what seemed improper choice of obstetric procedures to fit the cases, but that they were frequently the result of having applied these procedures too late in the course of labor.

An obstetric complication presenting a problem which not infrequently tests the judgment and skill of every obstetrician, is the patient in whom the cervix only partially dilates or fails to dilate as labor progresses. If the cervix dilates slowly, fetal distress may manifest itself before vaginal delivery is safe or possible. Before the onset of labor it is not easy to predict, with any degree of certainty, that this complication may arise. Various factors such as cephalopelvic disproportion, abnormal presentations and faulty positions of the presenting part are believed to predispose to its occurrence. However, in some women no cause can be found for this complication.

It is usually supposed that for some reason uterine contractions are either inefficient or that the cervix has some inherent anatomic or physiologic qualities which do not allow dilatation to occur. In some of these patients the quality of labor is good and obstetricians find reason to interfere when they decide that, after a satisfactory test of labor, delivery of a living baby by vagina is improbable. Other patients present a much more perplexing problem in that they have a true primary uterine inertia and some of their babies will show signs of fetal distress before uterine contractions have been sufficient in frequency or strength to constitute a legitimate test of labor.

Murphy's<sup>2</sup> observations with the tocograph may explain the reason for development of fetal distress in this type of labor. He has found that in the presence of primary uterine inertia, the uterine musculature sometimes fails to relax completely between contractions. A continued uterine muscular tonicity is the result, and it is possible that the baby suffers from a prolonged low grade anoxemia from interference with placental circulation. Eventually, before vaginal delivery is possible, death of the fetus in utero may occur.

It is interesting that this same complication, failure of the cervix to dilate, may or may not recur in subsequent labors in the same patient.

In our experience, methods recommended to correct difficulties encountered in these cases are not very successful. Obstetricians interested in the mechanism of labor in relation to pelvic architecture are convinced that means will be found to correct factors predisposing to uterine inertia and failure of the cervix to dilate. Endocrinologists are hopeful that they may soon have hormone products which will safely relieve uterine inertia. However, until an effective means is discovered to increase the safety of delivery of these patients by vagina and to prevent fetal deaths, the question is raised as to whether cesarean section can be made a sufficiently safe procedure to justify its use in such circumstances.

At the Woman's Hospital we are convinced that either cervical or extraperitoneal cesarean section skillfully performed in a proper ob-

Table XIII is a record of presentation and method of delivery employed in the 158 cases in which death of the fetus occurred during labor and delivery or in the neonatal period as a result of trauma and asphyxia.

Table XIV is a record of the indications and types of operations employed in the 35 cases delivered by cesarean section.

TABLE XIV. INDICATIONS AND TYPE OF OPERATION EMPLOYED IN THE 35 BABIES DELIVERED BY CESAREAN SECTION

INDICATIONS	TYPE OF OPERATION					TOTAL
	CLASS.	CERV.	EXTRA-PERIT.	PORRO	VAGINAL	
Placenta previa	1	8		1		10
Abruptio placentae	1	1				2
Cephalopelvic disproportion		4	2			6
Abnormal presentation						
Breech		1	1			2
Transverse		1		1		2
Cervical dystocia		1	2			3
Fetal distress		2				2
Cardiac disease		1				1
Myomas				1		1
Failure of induction					1	1
Previous cesarean	1	4				5
Total	3	23	5	3	1	35

Time of fetal deaths: Antepartum 6, intrapartum 8, neonatal 21, total 35.

Condition of babies before operation: Normal 22, in distress 7, dead 6, total 35.

Weight of babies: 1,500 to 2,500 Gm. 8, 2,500 Gm. and over 27, total 35.

Table XV shows the age at time of death of 139 babies that died within one month after birth. Forty-three per cent of these babies weighed less than 2,500 Gm. at birth and were therefore classified as premature. Nearly three-fourths of the neonatal deaths occurred within forty-eight hours after birth.

TABLE XV. DISTRIBUTION OF THE 139 NEONATAL DEATHS IN RELATION TO BIRTH WEIGHT AND AGE AT TIME OF DEATH

WEIGHT OF BABIES AT BIRTH	TIME OF NEONATAL DEATHS			TOTAL	PER CENT
	UNDER 24 HOURS	FROM 24 TO 48 HOURS	FROM 48 HOURS TO 1 MONTH		
1,500 to 2,500 Gm.	35	11	14*	60	43
2,500 Gm. and above	41	11	27	79	57
Total	76	22	41	139	100
Per cent	55	16	29	100	--

\*Includes one hydrocephalic baby that lived 105 days.

## DISCUSSION

In the analysis of this small series of fetal deaths, it has been obvious that many of our failures resulted from lack of success in handling some rather common obstetric conditions and complications.

In the past few years, some of our methods of handling certain obstetric complications have been gradually revised with the hope of increasing safety to mothers and avoiding some of the unfortunate

placenta is implanted in the lower uterine segment, most obstetricians are now agreed that cesarean section is the safest method of delivery. In our experience, delivery by the abdominal route combined with adequate replacement of blood loss and strict precautions against infection have markedly reduced the incidence of mortality from this complication in both mothers and babies.

In the treatment of abruptio placentae, we are called upon to treat a mild form in which simple rupture of the membranes and occasionally a hydrostatic bag yield satisfactory results, and the severe form which must be regarded as one of the most serious complications of pregnancy. In the hands of the most expert obstetricians, the severe form is attended by maternal mortality of at least 6 per cent and a high incidence of fetal deaths. Difference of opinion still exists as to the best method of treatment for this severe form. Some obstetricians favor the use of the Beck binder or the Spanish windlass and delivery by vagina. It is agreed that success in treatment of the severe form will depend upon control of bleeding and emptying the uterus as soon as possible. In our experience prompt cervical cesarean section offers the most logical and safest means of accomplishing both of these objectives. Incidentally this method is a lifesaving measure for some babies that would be lost in delivery by the vaginal route.

A considerable percentage of fetal deaths in this series resulted from unsuccessful management of labors and deliveries complicated by faulty positions of the presenting part, abnormal presentations of the fetus and cephalopelvic disproportion, the result of contracted pelvis or oversized babies.

It is not within the scope of this presentation to attempt to discuss the faults in management of all these varied conditions and complications which were responsible for many of the fetal deaths in the series that has been reported. Suffice it to say that results of treatment would have been better in some instances if certain important procedures had been followed.

Perhaps the most valuable obstetric contribution of this generation for safety of mothers and their babies has been the development and perfection of the stereoscopic method of roentgen pelvimetry. It offers a precise means for determining the size and conformation of the bony pelvis. By use of this diagnostic method, it is possible to predict with considerable accuracy what may be expected during the course of labor and as to whether delivery by vagina is possible or safe. By its use the decision to deliver certain patients by cesarean section can be made without the increased risk of operation after a prolonged test of labor.

The safety of a patient during labor and delivery could be promoted if obstetricians would make use of roentgen studies more frequently to check diagnosis when uncertainty exists as to the position and presentation of the fetus and when there is any question as to whether delivery by vagina is possible or likely to be attended with unjustifiable difficulties.

Prevention of tragic results in the outcome of labors and deliveries complicated by unusual positions of the presenting part, abnormal presentations or cephalopelvic disproportions require careful observa-

stetric environment is the safest method of delivery for both mothers and babies in some of these cases. Considerable obstetric judgment is required to decide whether and when these patients should be delivered by cesarean section. Faulty judgment may result in unnecessary cesarean sections or injured babies because delivery by the suprapubic route has been too long delayed.

In some patients with incompletely dilated cervices, if delivery becomes necessary in the interests of either the mother or baby, single or multiple cervical incisions are sometimes useful. However, this procedure cannot be employed without some danger of excessive bleeding and the risk of injury to important adjacent anatomic structures. This method should certainly not be used unless the head is well in the pelvis and the cervix is well thinned out and considerably dilated.

In 58 (26.9 per cent) of the labors in this series, which resulted in intrapartum or neonatal deaths, the fetal head engaged in an occipitoposterior position and had failed to rotate completely when delivery was attempted. In 33, the head was still in an occipitoposterior position, and in 25 it had rotated to a transverse position when delivery was undertaken. Eighteen or more than one-third of the 58 babies were in distress or dead before the decision to interfere had been reached. Twenty-seven of the 58 labors were prolonged as regards the first, the second, or both stages of labor.

In all that has been written regarding so-called conservative obstetrics, no condition has received more attention than occipitoposterior position. The advice has invariably been to leave the occiput posterior to nature, with the assurance that she would rarely require assistance if given sufficient time.

In former days when many women were delivered in their homes or in hospitals with inadequate obstetric facilities, this was undoubtedly sound obstetric teaching. However, in these days, when a high percentage of women are being delivered in well-equipped hospitals by expert obstetricians or under their supervision, will the practice of leaving all occiput posteriors to nature still yield the best results that can be had? If such labors progress well and the babies show no signs of distress, the treatment should be no different than that for anterior positions. However, if all women with occipitoposterior positions are carefully followed during the course of their labors, we are convinced that it is possible to select a certain small percentage in which timely operative interference is likely to be less harmful to the mothers and their babies than continuation of labors which are progressing too slowly.

If we are to prevent fetal deaths from conditions associated with occipitoposterior positions, the indication for operative interference should be unsatisfactory progress of labor rather than fetal distress. The records show that if this rule had been followed some of the fetal deaths in this series might have been avoided.

Twenty of the fetal deaths in this series occurred in women treated for placenta previa and premature separation of normally situated placentas. For patients with placenta previa who come under observation before the cervix has dilated and in those in whom considerable

5. Skillful and timely operative interference will reduce the incidence of birth injuries to some babies that survive as well as to those that die.

6. Provided women can be delivered in a good obstetric environment by skillful obstetricians, or under their direction, there is reason to believe that more babies and mothers will be injured by undue prolongation of labors that fail to progress than by timely operative interference.

7. It is possible that too much obstetric analgesia and anesthesia added to other contributory causes for intrauterine fetal asphyxia may be responsible for some fetal deaths or injured babies.

8. With widespread interest in obstetric results, it behooves obstetricians to reconsider their methods and to determine whether the accepted so-called conservative procedures can still always be depended upon to yield the best results.

9. Experience has shown that skillful application of the newer operative obstetric procedures for the protection of either mothers or their babies, have invariably reduced the hazards of labor and delivery for both. Results of the use of prophylactic forceps, and cesarean section for placenta previa, provide convincing evidence of the truth of this statement.

10. At least three-fourths of all fetal deaths, within the first month of life, are due to obstetric causes. Responsibility for their prevention is obstetric, in that it involves essentially prevention of premature births and management of labors and deliveries in ways to prevent fetal trauma and intrauterine asphyxia.

#### REFERENCES

- (1) Aldridge, Albert H., and Watson, Paul: AM. J. OBST. & GYNEC. 30: 554, 1935. (2) Murphy, Douglas P.: Surg., Gynec. & Obst. 70: 129, 1940.

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Pariser, Harry: Studies of the Transmissibility of Syphilis. The Infectiousness of the Vaginal Secretions and Menstrual Blood of Syphilitic Women, Am. J. Syph., Gonorr. & Ven. Dis. 25: 329, 1941.

Virulent *S. pallida* are discharged by the syphilitic woman into the vagina in the presence of local lesions early or chronologically "late" (more than four years' duration) in the course of the disease as a relapsing phenomenon. In the absence of such lesions, they are discharged only through the menstrual blood of the early syphilitic, or from an abnormal appearing cervix, in which instance it is probable that lesions are present within the cervical os or uterus.

Infectiousness through the vagina is periodically recurrent rather than continuously present in the syphilitic woman and depends upon the presence or absence of local lesions. The physiologic secretions are not infectious.

No data can be given as to the absolute end point of cervical relapse, and no estimate of the frequency of this relapse is available. In the author's series, infectious cervical relapse was found to have occurred at least six and one-half years after definite onset of the disease.

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tion of the progress of labor. The treatment of such patients should be carried on under the strict supervision of obstetricians who have had sufficient training and experience to know when interference is likely to yield better results than a continuation of labor. Results of the study that has been reported offer conclusive evidence that the choice of the optimum time for interference is just as important as the selection of a proper operative procedure to fit the case.

Twenty years ago it was not uncommon for an obstetrician to accept conditions and to adopt a method of delivery which was sure to result in a stillborn baby. This was sometimes based on the fact that "the patient was young and could try again." On occasion this course was followed in face of conditions which were likely to repeat themselves in subsequent pregnancies.

In recent years, we have been much interested in the prevention of maternal birth injuries. Most of these injuries are now preventable or can be successfully relieved by vaginal plastic surgery. However, perhaps the most serious birth injury in its effect on the health and happiness of a woman, is the emotional injury which comes through loss of a baby at birth and particularly her first. If a woman loses her first baby and for any reason is unable to conceive again, the result is often a tragic one. If she loses the first child, success in subsequent pregnancies never seems to provide sufficient compensation for the initial loss.

Conditions associated with pregnancy and particularly the first probably constitute the most profound emotional experience which comes to a woman within her span of life. It is probably fair to state that obstetricians have underestimated the seriousness of an unfortunate outcome of pregnancy from the emotional standpoint.

The medical profession is gradually learning the importance of emotional disturbances in relation to physical health. In the future, obstetricians may acquire a better understanding of the extent to which success in their efforts is likely to protect the health of women who suffer indirectly from emotional birth injuries.

#### SUMMARY

1. The causes of 271 fetal deaths that occurred on the obstetric service at the Woman's Hospital in a five-year period have been reviewed as to cause in relation to labor, methods of delivery, and certain aspects of maternal health.

2. Analysis of this series of fetal deaths showed that approximately one-fifth occurred in the ante-partum period, a little more than one-fourth during the course of labor, and about one-half within one month after birth.

3. Prematurity was the outstanding predisposing cause for these fetal deaths, and birth trauma and intrauterine fetal asphyxia were by far the most important actual causes of death.

4. Study of the causes of deaths reveals little that could have been done in either the ante-partum or neonatal periods to prevent their occurrence. It is obvious that our results can and must be improved by more judicious handling of women during labor and delivery.



Stated in another way, when an Rh negative woman carries in her uterus an Rh positive baby, in certain cases the baby's blood can stimulate the mother to form the anti-Rh agglutinin. This antibody, in turn, is able to pass back through the placenta and destroy the baby's Rh positive blood, thereby causing erythroblastosis. Should the mother be transfused with Rh positive blood, the agglutinin can agglutinate and destroy the transfused blood, the hemoglobin of which blocks the kidneys causing oliguria or anuria. This explanation of the pathogenesis of erythroblastosis has received statistical corroboration in a forthcoming paper.<sup>8</sup>

It should be noted, however, that there are exceptions<sup>7</sup> to this rule, since in certain cases of erythroblastosis the mother's blood also is Rh positive. These are not thought to be exceptions to the theory of immunization but rather to the Rh factor since other blood factors may be involved.

The association of erythroblastosis and transfusion accidents was first suggested by the following case\* which was observed in June, 1940.

#### CASE REPORTS

CASE 1.—Mrs. G. B., aged 32 years, had had one normal pregnancy terminated by forceps delivery (baby 9 pounds 9 ounces; no jaundice), and two spontaneous abortions. She was first seen in consultation because labor pains had stopped after fifteen hours of active labor at term; pain severe enough to disturb respiration had appeared in the right upper quadrant; and the fetal heart sounds had disappeared. The baby seemed large, the fetal head was not engaged, and the cervix was 1½ fingers dilated with a long uneffaced canal. With the diagnosis of a possible early rupture of the uterus, a cesarean section was performed. No rupture of the uterus was present and no cause for the pain in the right upper quadrant was found upon palpation of the liver and gall bladder. The baby was dead and weighed 10 pounds 7 ounces. The possibility of erythroblastosis was considered. This clinical impression was gained from the suggestion of edema about the neck and the absence of any more obvious cause for the stillbirth. No blood studies or autopsies were done.

Because of moderate anemia before operation (hemoglobin 60 per cent; red blood count 3,180,000) a 500 c.c. blood transfusion was given during and after the operation by the Baxter citrate method. The husband was used as a donor since both his blood and the patient's blood were of Group A (II Moss), and the cross-matching was satisfactory using the Landsteiner technique. A second transfusion (350 c.c. of Group A blood) was given that same evening because of symptoms suggestive of but not entirely characteristic of surgical shock. The following morning the patient was intensely jaundiced. Diminution of urinary output began on the first day postoperative, the patient excreting 350 c.c. in the first twenty hours after operation, only 3 drops in the next 11 hours, and only 60 c.c. in the following 24 hours. Urinary excretion improved somewhat thereafter but in only one 24-hour period did it exceed 500 c.c. (645 c.c. on the fourth day postoperative).

A third transfusion (400 c.c. of Group A blood) was given on the afternoon of the first postoperative day because of marked anemia (hemoglobin 46 per cent; red blood count 2,300,000). After temporary improvement and in spite of the absence of bleeding the patient became progressively more anemic (hemoglobin 40 per cent; red blood count 2,080,000 on the seventh day postoperative). Hence,

\*This case, together with those which follow, largely formed the basis for the theory and have been previously reported in less detail elsewhere.<sup>7</sup>

## THE COMMON ETIOLOGY OF ERYTHROBLASTOSIS AND TRANSFUSION ACCIDENTS IN PREGNANCY\*

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THE purpose of this communication is to call attention to the common etiology of two pathologic phenomena, the causes of which until recently have been obscure. These two apparently unrelated phenomena are erythroblastosis fetalis and certain transfusion accidents occurring in pregnancy. As will be explained in detail below, the etiology of erythroblastosis fetalis resides in an immunologic incompatibility between the fetus and the mother. In other words, there is present in the fetal red blood cells an antigen inherited from the father which is lacking in the mother. This antigen diffuses from the child into the mother's circulation, stimulating the formation of destructive antibodies. These antibodies like other maternal antibodies (for example diphtheria antitoxin) also diffuse readily into the fetal circulation where they can attack the red blood cells which contain the antigen, thereby causing erythroblastosis.

Should such a mother need a transfusion and should the transfused blood contain the antigen referred to, the destructive antibodies (agglutinins) in the mother's circulation agglutinate and hemolyze the transfused blood, thereby causing oliguria or anuria with its so often fatal consequences. These reactions occur between bloods of the same group and in spite of apparently compatible cross-matching.

This concept was developed from the following series of studies.

Atypical agglutinins have previously been found by Levine and Stetson,<sup>1</sup> among others.<sup>2, 3</sup> In their case of a transfusion accident following the delivery of a macerated fetus, the origin of the atypical agglutinin was for the first time suggested to be the immunization of the mother by the baby. According to their theory, the baby inherits a dominant blood property from the mother which is lacking in the father. The hypothesis that this immunization may also take place in certain cases of pregnancy with complications other than the retention of a dead fetus has also been advanced.<sup>4</sup>

In January, 1940, Landsteiner and Wiener<sup>5</sup> reported on an agglutinin which was developed in rabbits by the injection of blood from the *Macacus rhesus* monkey. When tested with human bloods this agglutinin demonstrated the presence of a new substance in human red blood cells which they called the Rh factor (Rh from rhesus). It has since been found that about 86 per cent of all human bloods<sup>6</sup> contain this factor (these are called Rh positive), and the remaining 14 per cent do not contain it (Rh negative). The agglutinin is called the anti-Rh agglutinin.

This agglutinin was first reported by Levine, Katzin, and Burnham<sup>7</sup> to be the destructive antibody responsible for the several manifestations of erythroblastosis. As stated by them, "one may assume that the (anti-Rh) agglutinins in the mother's circulation under certain conditions are capable of penetrating the placental barrier so that these antibodies, by their continual action on the blood cells and perhaps tissue cells of the fetus, induce erythroblastosis fetalis."

\*Read, in part, at a meeting of the Section of Obstetrics and Gynecology, New York Academy of Medicine, May 27, 1941.

All of the serologic studies in these cases were carried out by Dr. Philip Levine.

Within four months of the first case, another patient was observed in consultation (October, 1940). This was the case which crystallized the idea that there is a special danger of transfusion inherent in the mother of an erythroblastic baby. In addition, this was the first case of transfusion accident in a mother of an erythroblastic baby in which the anti-Rh agglutinin was found and identified (Case 3).

CASE 3.—Mrs. R. C., aged 32 years, had had 2 previous pregnancies both of which terminated with death of the baby. The patient stated that in 1934, after three days of labor at term, she was spontaneously delivered of a baby which weighed 6 pounds 4 ounces and lived only two hours. No cause for the death had been given to the patient, and it was assumed that trauma was the most likely cause.

Subsequent examination of the records of this delivery in another hospital revealed that the diagnosis given on the baby's death certificate was purpura hemorrhagica and that the autopsy diagnosis was incomplete expansion of the lungs with generalized edema and ascites. During a review of autopsy protocols four years later, this case was reconsidered and independently diagnosed erythroblastosis fetalis by the same pathologist who had done the original autopsy.

The second pregnancy occurred in 1937 and was terminated at about eight months by the delivery of a macerated hydrocephalic fetus, weighing about 6½ pounds. Fetal movements had been absent for two and one-half weeks. There were no signs of toxemia.

The present pregnancy progressed uneventfully and without any sign of toxemia. Eleven days before term an elective cesarean section was done with the hope of obtaining a living child. The baby weighed 6 pounds 12 ounces and was resuscitated with moderate difficulty. Within a few hours of birth it showed signs of pallor, beginning jaundice, and several fairly large blue areas in the skin. A blood count showed hemoglobin 36 per cent; red blood count 1,600,000; total nucleated cells (leucocytes plus nucleated red blood cells) 62,300; with 39 per cent polymorphonuclears, 37 per cent "lymphoblasts," and "many" nucleated red blood cells. The baby became progressively worse and died twelve hours after birth in spite of a blood transfusion of 50 c.c. from the father, given about six hours after birth. Autopsy showed areas of extramedullary hematopoiesis in the liver, spleen, and kidneys. Diagnosis: erythroblastosis fetalis.

Because of a considerable blood loss at the time of operation, a 500 c.c. blood transfusion was given at the close of the operation, using the husband as a donor. There was no chill or other obvious evidence of reaction after this first transfusion. During the immediate postoperative interval, the patient continued to bleed more than usual and her pulse was rapid and weak. On the first day postoperative the hemoglobin was 45 per cent and the red blood count 2,300,000. Therefore, the second transfusion of 500 c.c. was given on the afternoon of the first day, again using the husband's blood. There was no immediate sign of reaction, but one hour later there followed a severe pain in the abdomen and a shaking chill lasting thirty minutes.

Oliguria had already set in, the patient secreting only 200 c.c. during the first thirty-six hours postoperative. On the next four days the total urinary output was 30 c.c., 25 c.c., 45 c.c., and 60 c.c., respectively. The retention of nitrogenous end products was well advanced as early as the third day postoperative when the nonprotein nitrogen was 120. This reached a maximum on the sixteenth day when the nonprotein nitrogen was 350.

The danger of further transfusion was well appreciated. However, the need seemed great (hemoglobin 33 per cent; red blood count 1,240,000 on the second day), and it was thought that a compatible donor was available after careful selection by Dr. Levine. Therefore, 250 c.c. of blood was given on the fourth day. This likewise was followed in one hour by a severe chill.\*

\*The explanation for the use of this supposedly compatible but actually incompatible blood will be given in a later publication by Levine and Burnham.

a fourth transfusion (500 c.c. Group A blood) was given on the seventh day, and for the first time the transfusion was followed by an obvious reaction, namely chill and fever.

The patient became progressively weaker, developed a unilateral parotitis, and died early in the morning of the ninth day postoperative.

The likelihood of erythroblastosis fetalis being the correct diagnosis in this case as well as the association of erythroblastosis with the transfusion accident were strengthened by the similarity between the above case and one which occurred in 1938 (Case 2), with which my contact was mostly indirect.

CASE 2.—Mrs. J. B., aged 30 years, physician's wife, had had one previous pregnancy which terminated one and one-half years previously with a full-term hydrocephalic macerated fetus.

The present pregnancy had progressed normally until shortly before admission to the hospital at the end of the sixth month. Hospitalization was advised because of the absence of fetal heart sounds or fetal movements for six days, sudden enlargement of the abdomen, rapid gain in weight (15 pounds in two weeks), and slight generalized edema. Blood study on admission showed 35 per cent hemoglobin, 2,800,000 red blood count, and 5.0 icterus index.

On the day following admission at 3 P.M., a transfusion of 1,000 c.c. of blood was given, using two donors. Both donors, as well as the patient, were in Group O (IV Moss). This fact, as well as the compatibility in cross-matching, was later corroborated by four different investigators. Thirty minutes later the patient had a chill, and eight hours later she had an asthmatic type of dyspnea with cyanosis.

Uterine contractions began spontaneously that day. At 3:18 A.M. on the following morning the patient was spontaneously delivered of a macerated fetus which was markedly edematous and had an enlarged abdomen due to ascites. Birth weight was about 4 pounds. The placenta was edematous and two to three times the expected size. Autopsy of the baby showed the characteristic findings of hydrops fetalis.

As soon as daylight appeared marked jaundice was noticed (icterus index 200). The jaundice gradually subsided thereafter.

The patient excreted only 10 c.c. of urine during the twenty-four hours after transfusion. On the succeeding three days, the excretion amounted to 15 c.c., 30 c.c., and 90 c.c., respectively. Some improvement in this respect followed thereafter, but the daily total never exceeded 210 c.c. Blood chemistry showed marked retention of nitrogenous end products.

Notwithstanding, or because of the previous transfusion of 1,000 c.c. of blood, the patient became progressively more anemic. On the tenth day post partum, the hemoglobin was 20 per cent and the red blood count 1,300,000. Another transfusion was therefore considered imperative. A total of only 75 c.c. of donor's blood was given very slowly over a period of one and one-half hours. The patient developed asthmatic dyspnea and died about one hour later, on the tenth day post partum.

Partial autopsy showed marked edema of the lungs, bilateral massive pleural effusion and large white kidneys. The cause of death was stated as being acute hemolytic anemia of undetermined etiology with hemoglobinuric nephrosis, anemia, and uremia. It was thought that the hemolytic process had started shortly before admission, and that the first transfusion had precipitated it into full bloom.

All of the donors for these two cases as well as the husbands of both patients have since been tested and are now known to be Rh positive. Case 2 occurred two years before the Rh factor had been discovered, but in Case 1 there is evidence to indicate that the patient was Rh negative. In addition an atypical agglutinin was found in her blood on the fourth day post partum (Case 1), which we now have reason to believe was the anti-Rh agglutinin.

The baby (9 pounds 1 ounce) was pale at birth, had small petechial areas and larger bluish areas in the skin, and breathed very poorly. The blood count on the day of birth showed hemoglobin 40 per cent; red blood count 1,590,000; nucleated cells (white blood cells plus nucleated red blood cells) 198,000; polymorphonuclears 16 per cent, lymphocytes 5 per cent, megaloblasts 4 per cent, and normoblasts 74 per cent. Jaundice appeared twenty-four hours after birth. The baby was given two transfusions and improved rapidly thereafter, receiving 3 transfusions in all. The father's blood was used for all transfusions. The baby was discharged in good condition on the twenty-fourth day.

The anti-Rh agglutinin was found in the mother's blood serum on the sixth day. The mother was Rh negative and the father and baby were Rh positive.

Although the patient in the following case had neither an erythroblastic baby nor a transfusion, it is mentioned because it was the first pregnancy case published in the literature<sup>9</sup> in which the atypical agglutinin was identified as the anti-Rh agglutinin. Moreover, it seems likely that the abortions in the patient's previous history may have been due to the process of immunization. The explanation for the apparent lack of injury to the fetus in the last pregnancy, June, 1940, is not evident. What the effect of the many injections of progesterone might have been upon this is no more than conjecture.

CASE 5.—Mrs. H. H., aged 33 years, had had five previous pregnancies, in only one of which was the outcome satisfactory. In 1928 the first pregnancy terminated with a difficult forceps delivery resulting in intracranial injury, spastic paraplegia, and institutionalization of the child. Two years later a normal child was born by forceps delivery of a face presentation. There followed 2 spontaneous abortions in 1936 at six weeks and three months, respectively, and in 1938 at four and one-half months a third spontaneous abortion (fetus said to have been dead about one day).

The patient was most anxious to have another baby and presented herself before conception for examination and advice. The pregnancy occurred directly and continued to term. In the hope of avoiding abortion, she was given bi-weekly injections of progesterone from the fifth to the thirty-second week of pregnancy, totaling 44 injections almost all of which were of 5 mg. strength. Because the basal metabolism was normal, no thyroid extract was given. The diet was supplemented with extra-vitamins (no vitamin E however) and with adequate doses of iron.

On June 23, 1940, after three days of mild, irregular contractions at term and in the presence of a frank breech presentation with an unchanging, uneffaced cervix, a low flap cesarean section was done. The baby weighed 7 pounds 2½ ounces and showed no sign of erythroblastosis, although a blood count soon after birth was not done.

Preliminary blood examination had shown that both the patient and her husband were in Group A, but that the cross-matching was definitely incompatible. Since this occurred at the same time that Case 1 was under observation, specimens of their bloods were sent for further study. This revealed in the patient's serum the presence of an atypical agglutinin and identified it as the anti-Rh agglutinin.<sup>9</sup> The patient was later found to be Rh negative, and her husband and baby Rh positive. Fortunately a transfusion was not needed. The mother and baby were discharged from the hospital in good condition on the fourteenth day post-operative.

#### DISCUSSION

The incidence of erythroblastosis has been given as one in every 2,000 confinements. This includes the three accepted clinical forms, namely hydrops fetalis, icterus gravis, and congenital anemia of the newborn. In recent years it has been realized that the disease is more frequent than was formerly thought. Thus Wolfe and Neigus<sup>10</sup> reported an

In the meantime efforts to obtain large amounts of pooled plasma were finally successful. Starting on the fourth day the patient received 6,150 c.c. of plasma (already diluted half and half with physiologic salt solution) during six days until the patient's plasma protein determinations reached the normal level. This was supplemented with large doses of molar sodium lactate and concentrated glucose in distilled water until the marked acidosis was corrected. It seems very likely that the patient's ultimate recovery can be attributed in large part to the use of the plasma which gave the patient large amounts of the essential fluid constituents of the blood even though the cellular elements were lacking.

The patient's condition was such that she was able to withstand a unilateral parotitis (onset eighth day) and a bilateral bronchopneumonia (onset ninth day) in addition to the marked uremia; albeit for several days the margin seemed very slim.

The hoped-for improvement in urinary output began on the eleventh day when 250 c.c. were excreted. This was followed on succeeding days by 500 c.c., 865 c.c., 1,375 c.c., 1,870 c.c., 3,100 c.c., and 4,425 c.c. The latter two days and the following four days were the only ones on which the urinary output exceeded the fluid intake, and during these six days the moderate peripheral edema largely subsided.

During the course of the case, blood studies were being constantly carried on. The patient was found to be Rh negative, and the baby, the husband, and the first three transfusion donors were Rh positive. The anti-Rh agglutinin responsible for the destruction of donor's blood was first demonstrated in the patient's serum on the eighth day. On the twelfth day the first Rh negative donor was used (500 c.c. in two divided doses) without a reaction of any kind. Another 500 c.c. of slightly incompatible blood was given on the fifteenth day and followed by a chill.\* Two days later the patient was still very anemic (hemoglobin 34 per cent; red blood count 1,580,000). Thereafter three transfusions, each of 500 c.c. of Rh negative blood, were given on the eighteenth, twentieth, and twenty-third days, respectively, without any reaction. The patient was now recovering rapidly after having regained consciousness on the twentieth day. She was discharged from the hospital, strong enough to walk a few steps, on the thirty-sixth day.

The following case occurred about one month after Case 3.

CASE 4.—Mrs. E. F. W., aged 38 years, had one spontaneous abortion at eight to nine weeks in 1937, two laparotomies for sterility (one for uterine suspension and appendectomy and one for adhesions), and one previous cesarean section. The second pregnancy had been terminated in 1938 by cesarean section because of a male pelvis with a brow presentation in an elderly primipara. At that time the uterus failed to contract well and the patient was transfused immediately after the operation with 600 c.c. of her husband's blood without any reaction. The baby weighed 8 pounds 3 ounces and had no jaundice or other sign of erythroblastosis.

During the present pregnancy there was some edema of the face and feet, but no other sign of toxemia (weight gain 18 pounds, highest blood pressure 128/84, and no albuminuria). A secondary anemia was present which improved under iron therapy (hemoglobin 65 per cent rose to 80 per cent).

A second cesarean section was done (Nov. 30, 1940), the uterus again failed to contract well and a transfusion of 500 c.c. was given immediately after the operation, again using the husband as a donor. There was no immediate reaction and in fact none for the first three days postoperative. However, on the fourth day, oliguria set in, the urinary output being only 300 c.c. On the following 4 days it was 270 c.c., 510 c.c., 420 c.c., and 180 c.c., but marked improvement began thereafter. On the seventh day there was a considerable nitrogen retention (blood urea nitrogen 81.5) and other signs of uremia. The patient made a gradual recovery, the blood chemistry returning to normal on the twenty-third day.

\*See footnote on page 392.

incidence of 1 in 568, and Javert<sup>11</sup> has found it to be 1 in 400. In the last 1,400 deliveries at the Englewood Hospital we have had 8 cases, an incidence of 1 in less than 200. This is a small series and probably represents a selected sample. However it should be noted that 6 of these 8 cases would have been missed had we not been on the lookout for them, and had not our suspicion been confirmed by the blood studies of Dr. Levine. Of the 6, 2 would have been considered fetal deaths in utero of unknown cause (macerated fetuses), and the remaining 4 would have been considered idiopathic anemias of the newborn, inasmuch as blood smears were made too late to show erythroblasts, and all 4 recovered after transfusions.

Thus it is apparent that the erythroblastosis group must be broadened to include some of the macerated fetuses not due to syphilis, diabetes, or toxemia, and also many if not most of the anemias of the newborn. Some cases of miscarriage likewise belong in the group.

The danger of transfusion for the mother of a baby with erythroblastosis becomes evident. We formerly thought of transfusion accidents only in terms of faulty grouping. The statement has even been made that cross-matching of donor and recipient's blood was unnecessary if one were certain of using the same blood group. But reactions between bloods of the same group have been reported with increasing frequency.<sup>12</sup> This is because the Rh factor and the anti-Rh agglutinin react within the same blood groups, since they are unrelated to the blood groups. When the anti-Rh agglutinin is present, cross-matching in the usual manner often fails to reveal the existing incompatibility. In another case (J. L.<sup>7</sup>), cross-matching between the patient and her husband was carefully done by two commonly accepted methods without detecting any incompatibility, even though it was known to be present.

In the series of 8 cases mentioned before, 2 of the patients were transfused with blood from the same group, and each suffered a fatal or near fatal reaction. Of the 6 other cases, 3 were found to have developed the anti-Rh agglutinin in their blood and likewise would very probably have had severe reactions if transfused. Two of the remaining 3 cases were investigated so long after delivery (six and twelve months, respectively) that the agglutinin might well have disappeared from the blood stream. This leaves only one of the 8 cases in which the danger of transfusion was no more than potential.

Probably the most important aspect of these morbid states is their prophylaxis. In erythroblastosis, we know nothing of the circumstances which permit the immunization of an occasional Rh negative mother by an Rh positive baby and not the immunization of the vast majority of such mothers. Nor can we explain why in the case of H. H., the anti-Rh agglutinin was formed in the mother but caused no apparent harm in the baby. Therefore the prevention of erythroblastosis is still unsolved. Fortunately many of the babies live long enough to be cured by transfusion, provided they are recognized in time.

On the other hand much can be done to prevent a transfusion accident in the mothers with its almost 50 per cent mortality. It is believed that almost all if not all of these reactions can be prevented by a modified cross-matching technique devised by Levine.<sup>6</sup> This consists of the incu-

TABLE I. RÉSUMÉ OF CASES

CASE	AGE	GRAVIDITY	LIVING CHILDREN	Rh	ANTI-RH AGGLUT.	Rh HUSBAND	Rh BABY	BABY OUTCOME	REMARKS
G. B.	32	iv	1	Neg.	Present	Pos.	?	Macerated fetus, erythroblastosis ?	4 transfusions Rh pos. blood, jaundice, anuria, uremia, death ninth day
J. B.	30	ii	0	?	?	Pos.	?	Macerated fetus, erythroblastosis	1 transfusion 1,000 c.c. Rh pos. blood, jaundice, anuria, second transfusion 75 c.c. Rh pos. blood 1 hr. before death tenth day
R. C.	32	iii	0	Neg.	Present	Pos.	Pos.	Lived 12 hr., erythroblastosis	3 transfusions Rh pos. blood, reaction, anuria, uremia. Recovery after 6,150 c.c. plasma and 1,500 c.c. Rh neg. blood
E. F. W.	38	iii	1	Neg.	Present	Pos.	Pos.	Erythroblastosis, recovery after 3 transfusions	1 transfusion Rh pos. blood, delayed oliguria, uremia. Recovery
H. H.	33	vi	2 (one spastic paraplegia)	Neg.	Present	Pos.	Pos.	Normal baby	Incompatible cross-matching between patient and husband, no transfusion



# PARENTERAL VITAMIN K THERAPY IN ANTE-PARTUM WOMEN AND ITS EFFECTS ON THE INFANTS' PROTHROMBIN LEVELS

## A PRELIMINARY REPORT

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MOST of the experimental work done thus far on vitamin K therapy in obstetrics and pediatrics has concerned the oral use of vitamin K in women not in labor and in infants after delivery. In the series of cases described in this report, we have sought to determine the effectiveness, particularly in infants, of parenteral vitamin K therapy administered to pregnant women before the onset of, and during, labor. Our objectives were to determine:

1. Whether parenteral vitamin K therapy affects the prothrombin level of the blood of pregnant women; and whether such therapy influences the prothrombin levels of newborn infants immediately post-partum, and during the first few days of life.

2. The optimum time of administration in the period preceding delivery; and the effective dose of the preparation used.

Vitamin K therapy was applied in the form of 2-methyl-1, 4-dihydroxynaphthalene diphosphoric acid ester tetrasodium  $(\text{C}_{10}\text{H}_6\text{O}_2\text{PNa}_4 \cdot 6\text{H}_2\text{O})$   
"882" 2

salts,\* hereafter referred to as Preparation N-123. The antihemorrhagic activity of this preparation has been reported by Foster and Lee and others.<sup>1, 2</sup> It was found to be about 50 per cent more potent than methyl naphthoquinone. Toxicity studies of this preparation in animals<sup>3</sup> show no harmful effects with doses much larger than the therapeutic dose. This vitamin K-like principle is a clear water-soluble preparation. It may be administered orally, subcutaneously, intramuscularly, or intravenously. In our study, the drug was injected intramuscularly in doses of 10 mg. or larger. No local or systemic by-effects or untoward reactions were noted.

## METHODS

The blood prothrombin levels were determined in 4 pregnant women (Group I) by the plasma method of Quick,<sup>4</sup> a two-stage method. All other prothrombin de-

\*A synthetic substance prepared by Hoffmann-LaRoche, Inc., Nutley, N. J., who kindly provided the necessary supplies for this study in 1 c.c. ampoules of an aqueous solution, 10 mg. each.

bation of the mixture of donor's cells and recipient's serum at body temperature for thirty minutes. The mixture is then centrifuged and read as in the usual Landsteiner method. There is no reason why this modification cannot be easily performed in any laboratory. The time element involved (thirty minutes) is no more than is usual with some other techniques. It is usually safer to delay the transfusion thirty minutes than run the risk of an irreversible hemolytic reaction.

Should a mother of a possible erythroblastosis baby require a transfusion, it is safer to determine the Rh status of the mother and use a corresponding donor as already pointed out. Usually this will be an Rh negative donor. Should none of these precautionary measures be available in a given suspicious case, it is safer to use blood substitutes, preferably blood plasma.

### CONCLUSIONS

1. Erythroblastosis fetalis is due to the destruction of the baby's blood by the *anti-Rh agglutinin*, which has been formed in the mother's blood by immunization of an Rh negative mother by an Rh positive baby.

2. Severe transfusion accidents in the mothers of erythroblastic babies are exceedingly common and likewise are due to the destruction of the donor's blood by the anti-Rh agglutinin.

3. These reactions are almost always if not always preventable, by means of a modified cross-matching technique.

4. The mothers of erythroblastic babies may be safely transfused preferably after determination of their Rh status, and usually by the use of Rh negative blood.

5. Erythroblastosis is more common than generally appreciated.

6. The group includes cases other than the three accepted clinical forms of hydrops fetalis, icterus gravis, and congenital anemia of the newborn.

7. Early blood counts of suspicious babies (early jaundice and/or anemia) will permit the saving of many babies by transfusion.

The author is indebted to Drs. R. L. Barrett, J. G. Gershman, J. W. Prather, and H. W. Taylor for the privilege of presenting their cases.

### REFERENCES

- (1) Levine, Philip, and Stetson, R. E.: J. A. M. A. 113: 126, 1939.
- (2) Zacho, A.: Hospitalstid. 78: 225, 1935; Ztschr. f. Rassenphysiol. 8: 1, 1936.
- (3) Wiener, A. S., and Peters, H. R.: Ann. Int. Med. 13: 2306, 1940.
- (4) Levine, Philip, and Katzin, E. M.: Proc. Soc. Exper. Biol. & Med. 45: 343, 1940.
- (5) Landsteiner, K., and Wiener, A. S.: Proc. Soc. Exper. Biol. & Med. 43: 223, 1940.
- (6) Levine, Philip: AM. J. OBST. & GYNEC. 42: 165, 1941.
- (7) Levine, Philip, Katzin, E. M., and Burnham, Lyman: J. A. M. A. 116: 825, 1941.
- (8) Levine, Philip, Burnham, Lyman, Vogel, Peter, and Katzin, E. M.: In preparation.
- (9) Levine, Philip, Katzin, E. M., and Burnham, Lyman: Proc. Soc. Exper. Biol. & Med. 45: 346, 1940.
- (10) Wolfe, Samuel A., and Neigus, Irwin: AM. J. OBST. & GYNEC. 40: 31, 1940.
- (11) Javert, C. T.: Ibid. 34: 1042, 1937.
- (12) Dieckmann, William J., and Kramer, S.: Ibid. 40: 61, 1940.

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Our experimental group comprised 27 normal pregnant women chosen at random from the prenatal clinic. The majority delivered spontaneously or were delivered by low forceps. They were divided into five groups as follows:

*Group I:* 5 ante-partum women. Vitamin K therapy was instituted as near the estimated date of confinement as possible. Ten milligrams of N-123 were given by intramuscular injection daily for six days in three cases; for three days in one case (Pt. 4); and for two days in one case (Pt. 5). Prothrombin determinations were made before administration of the drug, and daily during its use.

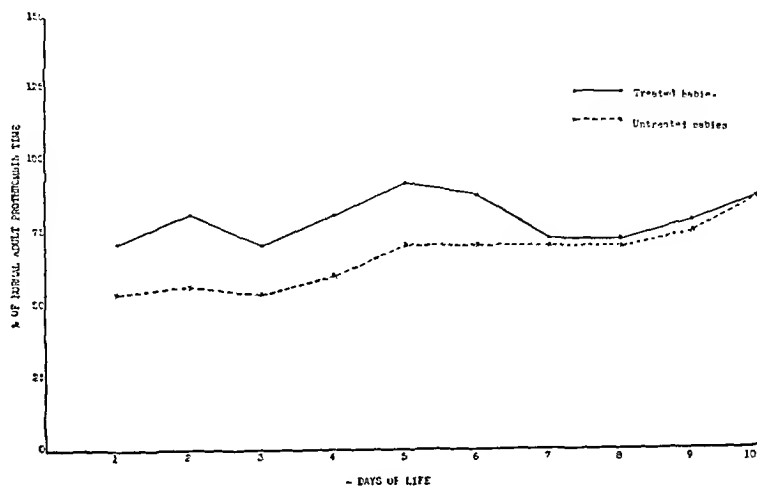


Fig. 3.—Composite curve: Prothrombin levels of 4 infants born to mothers receiving a single dose of 10 mg. of Preparation N-123 within one to seven hours before delivery.

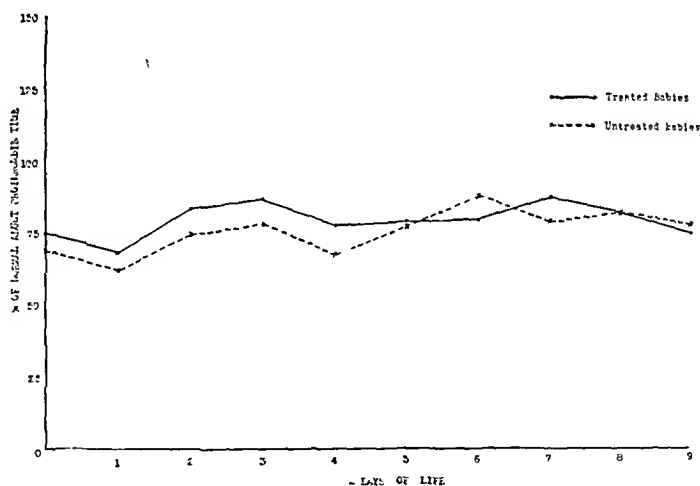


Fig. 4.—Composite curve: Prothrombin levels of 12 infants born to mothers receiving a single dose, 20 mg. of Preparation N-123 by intramuscular injection within twenty minutes to twenty-one hours before delivery (includes determination in 3 infants whose prothrombin levels were not affected). The effect, evident at birth, wears off at about the fifth day.

1. The pre-injection prothrombin levels were within normal limits in the mothers in this group; and, as was to be expected, administration of the drug did not significantly change the prothrombin levels (Fig. 1).

2. The prothrombin levels of the infants born of these mothers who had received injections of vitamin K terminated several days before delivery (from two to twelve days) showed no definite elevation compared with control infants born of

terminations were done by the micromethod of Quick,<sup>5</sup> slightly modified as follows:

Five-hundredth cubic centimeter of a thromboplastin solution\* was measured from a small carefully graduated pipette into a clean 10 by 70 mm. test tube at room temperature; 0.05 c.c. of blood freshly drawn from a finger or heel puncture was added, and the tube was gently agitated to insure mixing. The time required for clot formation was noted on a stopwatch. This was taken as the blood prothrombin time. Duplicate determinations were run on each case, and invariably they checked within two seconds.

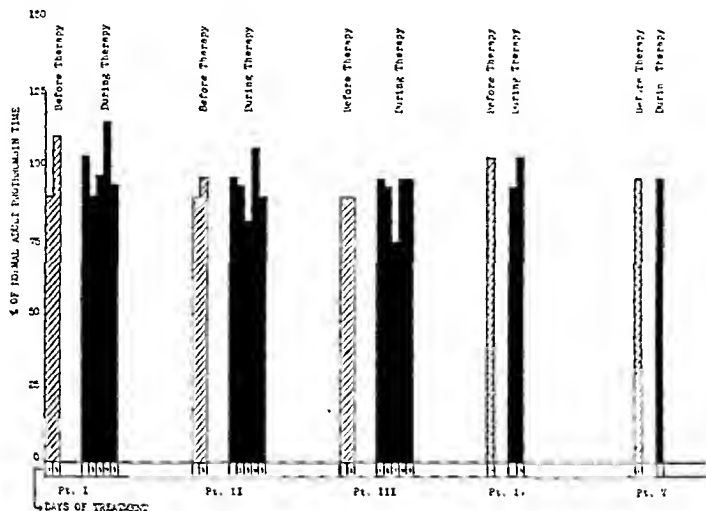


Fig. 1.—Prothrombin levels of ante-partum women receiving parenteral vitamin K therapy several days before labor. Ten milligrams of Preparation N-123 daily by intramuscular injection.

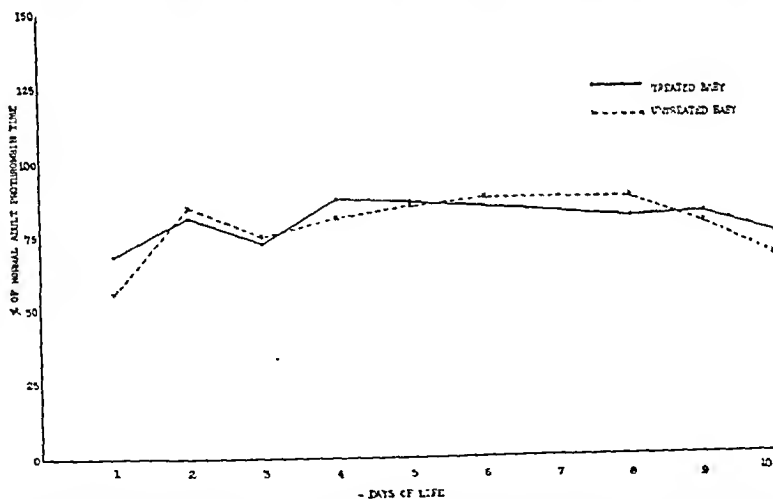


Fig. 2.—Characteristic curve: Prothrombin level of infant born to Patient 1, Group I, who received 6 daily doses, 10 mg. each, of Preparation N-123. Last dose: one week before delivery. No definite effect.

The prothrombin time of the ante-partum women, expressed in percentages of the prothrombin time of normal adult controls, were determined before and after injections of Preparation N-123 (Fig. 1). In the infants, the prothrombin determinations were made as nearly as possible at the same time of day throughout the tests. For control purposes, the same determinations were made, (1) in infants born approximately at the same time but of untreated mothers; and (2) in normal adults, usually post-partum women in the ward.

\*Thromboplastin solution was prepared from powdered rabbit brain (thrombokinase) furnished in ampoules by Difeo Company.

*Group III:* 12 ante-partum women. In these cases, we sought to determine if there was any greater effect obtained by increasing the dose of vitamin K. A single injection of 20 mg. of Preparation N-123, was given intramuscularly within twenty minutes to twenty-one hours before delivery.

The prothrombin levels of 75 per cent of the infants born of these mothers (9 cases) were definitely elevated, and 25 per cent (3 cases) showed no changes. Figs. 4 and 5 show the curves averaged from these cases, and it will be noted that they resemble the curves in Group II. We have no explanation to present for the lack of effect observed in 3 cases.

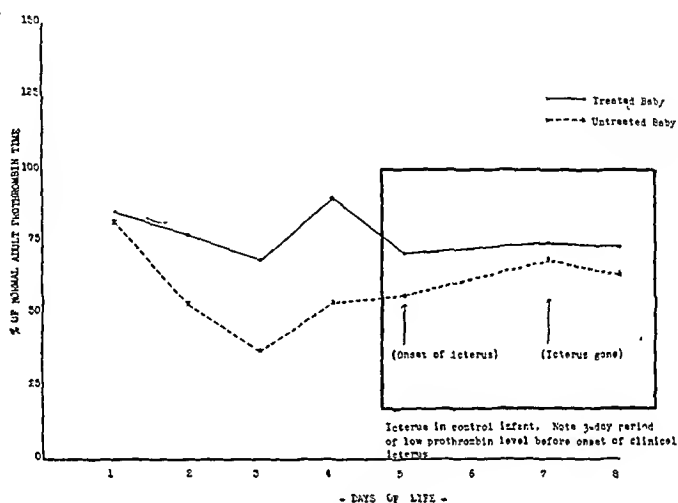


Fig. 7.—Single case, Group IV. Prothrombin level of infant born to mother receiving a single dose, 30 mg. of Preparation N-123 by intramuscular injection one and one-half hours before delivery.

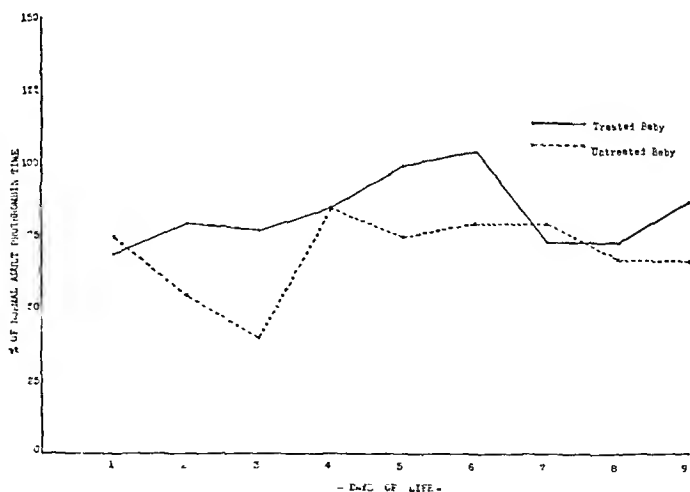


Fig. 8.—Prothrombin level of infant born to mother receiving two doses, 10 mg. each, of Preparation N-123 by intramuscular injection. First dose, twenty-three hours before delivery; second dose, eleven hours before delivery.

*Group IV:* 3 ante-partum women. In two of these cases a single intramuscular injection of 30 mg. of Preparation N-123 was given before delivery. In one case the injection was made one and one-half hours prior to delivery; and in the second case five and one-fourth hours before. The third patient received a larger dose, 40 mg. of N-123, in a single injection four and one-half hours before delivery.

untreated mothers. Fig. 2 illustrates a typical case where the maternal administration of the drug was terminated one week before delivery occurred.

In view of the results observed in Group I, it was decided to administer the vitamin K-like principle to women in labor, and to study the effects on the infant prothrombin level when the dosage was increased and the time interval before delivery was reduced.

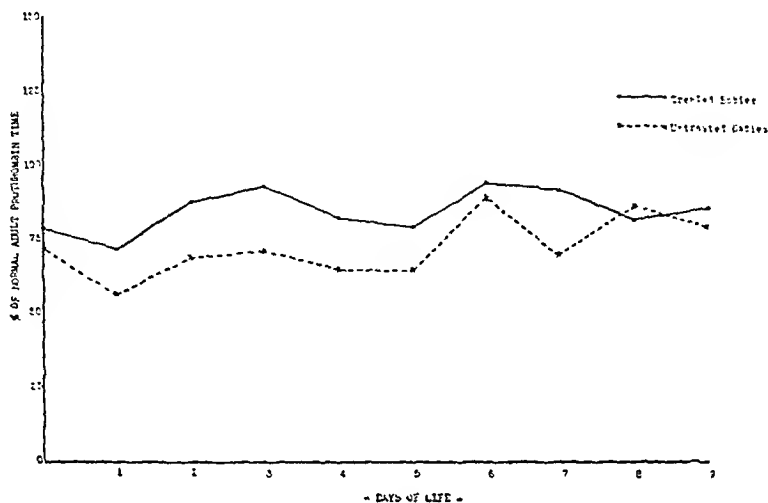


Fig. 5.—Composite curve: Prothrombin levels of 9 infants born to mothers receiving a single dose, 20 mg. of Preparation N-123 by intramuscular injection within twenty minutes to twenty-one hours before delivery.

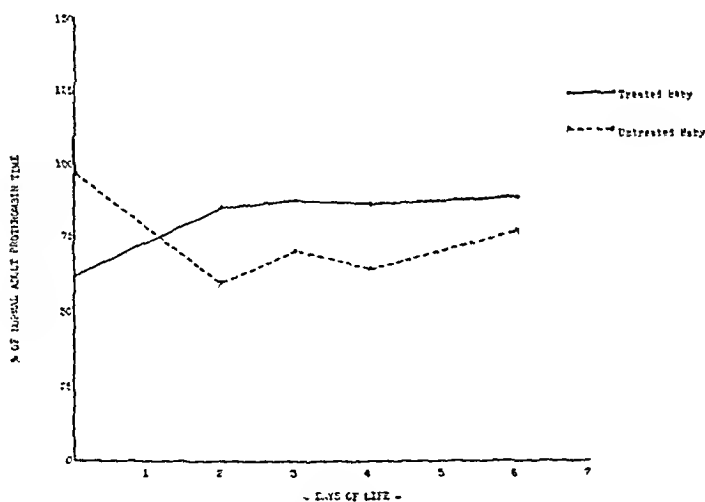


Fig. 6.—Single case, Group III. Prothrombin level of infant born to mother receiving a single dose, 20 mg. of Preparation N-123 by intramuscular injection twenty minutes before delivery illustrates rapid absorption from maternal circulation.

Group II: 4 ante-partum women. Vitamin K therapy was instituted during labor. A single dose of 10 mg. of N-123 was injected intramuscularly one hour before delivery in one case, six hours before in one case, and seven hours before in two cases.

The prothrombin levels of infants born of these mothers were significantly changed compared with infants born of untreated mothers. In Fig. 3, the results are averaged, and it will be noted that there is about a twenty per cent increase in the prothrombin levels of the treated infants the first day of life, and that this effect is maintained for about six days.

If delivery does not occur within a few hours after injection, the effect is less; the substance is probably destroyed or excreted by the maternal system. It would seem advisable therefore to repeat the injection shortly before delivery.

It is generally admitted that intracranial hemorrhage in infants probably occurs before or during delivery. If it is possible to elevate the infant's prothrombin level in utero by administering vitamin K to the mother in a rapidly absorbable form, this should be more effectual than treating the infant after delivery.

(Further studies are being made with Preparation N-123 in an endeavor to observe its effects on the prothrombin levels when injected in infants immediately after birth.)

We wish to express our appreciation to Dr. Adolph Bernhard for his modification of the Quick microprothrombin method as described in this paper.

#### REFERENCES

- (1) *Foster, R. H. K., Lee, J., and Solmssen, U. V.*: J. Am. Chem. Soc. 62: 453, 1940. (2) *Lee, J., Solmssen, U. V., Steyermark, Al., and Foster, R. H. K.*: Proc. Soc. Exper. Biol. & Med. 45: 407, 1940. (3) *Foster, R. H. K.*: Ibid. 45: 412, 1940. (4) *Quick, A. J.*: J. A. M. A. 110: 1658, 1938. (5) *Idem*: Proc. Soc. Exper. Biol. & Med. 42: 788, 1939.

### VITAMIN A IN PREGNANCY\*

#### II. COMPARISON OF DARK ADAPTATION AND SERUM TESTS

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THIS is the second of a series of studies to determine the value of fortifying prenatal diet with artificial vitamins as indicated by both subjective and objective tests for vitamin A among clinic pregnancies under better than average dietetic management.

Vitamin A was selected for several reasons: (1) Relatively practical tests; (2) clinical manifestations of deficiency due to keratinizing epithelial metaplasia of the alimentary (glossitis, parotitis, etc.), respiratory (tracheobronchitis), urinary (pyelocystitis), ocular (xerophthalmia and cutaneous (keratosis pilaris) systems; (3) possible relation to liver dysfunction (pre-eclampsia) due to liver storage, and to puerperal morbidity due to epithelial change.

The studies are based on the assumption of general population deficiency of vitamin A intake according to the complete report of Lehman and Rapaport<sup>1</sup> who reviewed clinical manifestations of deficiency among soldiers, prisoners, and asylum inmates, as well as among medical students, and also dietetic deficiency among 66 per cent of 4,000 working

\*Read at a meeting of the Obstetrical Society of Philadelphia, March 6, 1941.

1. The prothrombin levels of the two infants born of the mothers receiving the 30 mg. doses were definitely elevated; in the single case receiving 40 mg. no effect was noted.

2. The results in these cases where larger doses of vitamin K (20, 30, and 40 mg.) were used showed no greater elevation of the infants' prothrombin levels than the cases in Group II where 10 mg. doses were employed.

3. The effectiveness of parenteral administration of this vitamin K principle in regard to time intervals before delivery is shown in Fig. 6. This shows elevation of the prothrombin level in a case where the drug was injected only twenty minutes before birth of the baby. The drug seems less effective if more than about 15 hours have elapsed between the time of injection and delivery.

4. The curve of one of the patients in Group IV who received 30 mg. of N-123 one and one-half hours before delivery is shown in Fig. 7. Definite effect is evident in the treated case, and it is also of interest to note in the control infant, who developed clinical physiologic jaundice of the newborn, that the extremely low blood prothrombin level antedated the icterus by two days.

*Group V:* 3 ante-partum women. These patients all had prolonged labors, one case being terminated by a midforceps delivery. In two cases, a 10 mg. dose of N-123 was given early in labor and repeated once in each case about ten hours later. The third case, which was the instrumental delivery, received 3 injections of 10 mg. each of the drug at twelve hourly intervals during a fifty-hour labor, and delivered twelve hours after the last injection.

One case (Fig. 8) showed definite elevation of the prothrombin level of the baby born of the treated mother. The second case, although the last dose of the drug was given only three hours before delivery, showed only slight prothrombin level elevation, and the case in which midforceps was employed showed no effect. At present we have no explanation for the lack of action in these two cases.

#### SUMMARY

1. Parenteral vitamin K therapy does not seem to affect the normal prothrombin level in pregnant women.

2. If a course of parenteral vitamin K therapy is terminated several days before delivery, the prothrombin level of the infant is not affected.

3. Parenteral vitamin K therapy given during labor caused definite elevation of the blood prothrombin level in 16 of 22 infants (73 per cent).

4. Use of doses of vitamin K larger than 10 mg. produced no greater elevation of the prothrombin level.

5. Elevation of the infant's prothrombin level seems to occur very quickly after injection in the mother. If more than fifteen hours elapse between injection of the drug and delivery, the effect seems to be decreased.

#### CONCLUSIONS

In this study a new water-soluble vitamin K-like principle has been administered parenterally to ante-partum women, and its effect on the prothrombin levels of the infants has been determined.

The drug apparently does not alter the normal prothrombin level of the mother, but its effects in the infant seem to be manifested promptly after injection. Therefore we may assume placental transmission of this substance occurs.



To determine the above question, we present a second study in two parts: (1) Mostly single, corrected, dark adaptation tests of 328 elinie pregnaneies under precisely the same conditions as before; (2) a small series of 34 pregnaneies tested for blood serum vitamin A by the Clausen and McCoord method, as well as by adaptometer.

According to Fig. 1, there is less actual "night blindness" (over five minutes) than in our first series, but generally higher readings due no doubt to mostly single tests. There were only 7 (2.13 per cent) values above five minutes from 340 readings out of 328 patients, but 5 of these were primary false readings, subsequently normal, so that the remaining 2 consistently high cases represent but 0.62 per cent abnormals. Of these 2, 1 was entirely uncomplicated, and 1 showed only pre-eclampsia, whereas there were 23 instances of toxemia among the remainder, among whom there were also 6 cases of anemia with hemoglobin below 60 per cent (Dare). There were no other significant complications in this group, except one case of cutaneous papillary keratosis.

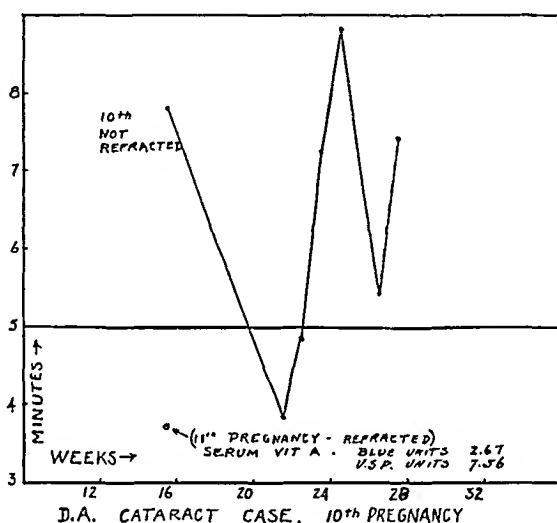


Fig. 3.—False high adaptometer readings in tenth pregnancy due to eyestrain. Normal reading in eleventh pregnancy (lower) with vision corrected, but false blood test for vitamin A.

Fig. 2 shows the results of blood serum tests for vitamin A according to the method of Clausen and McCoord.<sup>5</sup> This test is a fairly complicated colorimeter differentiation between petroleum ether extraction from serum of 15 c.c. of blood, of carotinoids and vitamin A by potassium dichromate and antimony trichloride, respectively. The amount of vitamin A is calculated as arbitrary (blue) units, representing 2.8 U.S.P. units per 100 c.c., allowing considerable deviation.

Our single calculations showed excessively wide excursions due to lack of experience as well as to difficulty with carotinoid yellow in the colorimeter, but if accepted as a relative test, indicate frequent (40 per cent) deficiency with no correlation whatever to the adaptometer readings.

For evaluation, the clinical applications of Clausen and McCoord are important, from study of newborns, infants under six months, six to twenty-four months, and over two years, from which they found a fall of serum vitamin A due to fever proportionate to that due to low carotene diet. They found high blood carotene in normal, diabetic and hypothyroid subjects with xanthosis cutis, but similar

families as reported by the U. S. Labor Bureau. Holman<sup>2</sup> likewise found 26 per cent of 38 patients admitted to the Stanford-Lane clinic for medical-surgical care markedly deficient according to the Hecht Adaptometer, and called attention to the vital necessity of vitamin A saturation to prevent postoperative infections (parotitis, bronchitis, pneumonia, and pyelocystitis). Williams and others<sup>3</sup> also recently found dietetic A deficiency in 62 per cent of 123 pregnant clinic women, with 37.5 per cent abnormal dark adaptation without correlation.

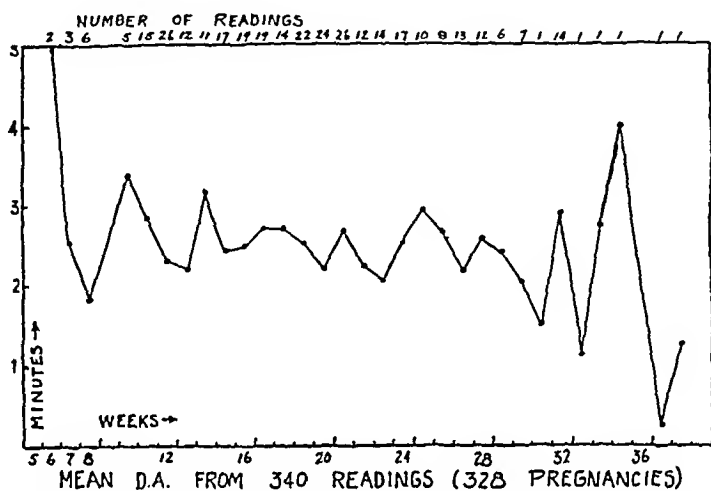


Fig. 1.—Normal adaptometer averages among pregnant women under good conditions.

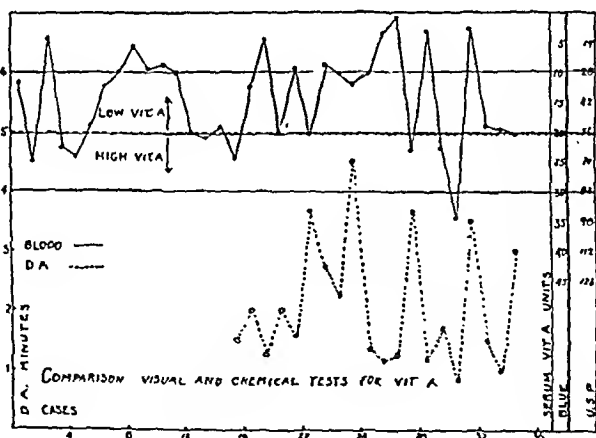


Fig. 2.—Extremely variable blood vitamin A (upper) of 35 pregnancies, compared with normal adaptometer readings (lower). Fifty additional blood tests also showed excessive variations.

Our prior observations<sup>1</sup> from 880 adaptometer tests among 200 pregnancies under good prenatal care showed much less deficiency than generally reported, i.e., 9 per cent gross, 3 per cent corrected, and 4 per cent borderline cases. Since 6 per cent gave an initial false-positive deficiency test, subsequently normal, we stressed the necessity of repeating all abnormal readings and assumed either that the accuracy of the method was questionable or that increased appetite and improved diet of our patients resulted in scant vitamin A deficiency in pregnancy.

We considered our series too small to draw conclusions with reference to subnormal vitamin A intake and febrile morbidity in the puerperium. It has been noted, however, in Wales that the distribution of accessory foodstuffs to indigent pregnant women in the Rhonda Valley bringing their vitamin A intake to above normal was followed by a much lower incidence of sepsis, than in comparable untreated series.

In our study we did not have access to a physiologic chemist, and we were unable to add a study of the blood content of vitamin A. Very recently, however, Pett and LePage and Steininger, Roberts and Brenner have correlated in two studies the diet content of vitamin A, dark adaptation time, and the blood content of vitamin A. Pett and LePage regard the blood level of vitamin A as a variable, dependent on the absorption and transference of vitamin A in the tissue, and conclude that adaptation time is not sufficiently sensitive to detect these changes. They noted some evidence of diurnal rhythm for vitamin A in the blood. Pett and LePage found that a definite correlation existed between the vitamin A in the blood and vision tests for vitamin A deficiency. On the other hand Steininger and her group in Chicago felt that that amount of vitamin A in the fasting blood is directly affected by the amount of vitamin A in the diet and that the blood level depends upon the previous day's diet as well as upon the habitual intake. They do not feel that the blood level at any given time would necessarily reflect the body stores of the substance. They conclude in contradiction to Pett and LePage that no correlation exists between the vitamin A in blood and the biophotometric readings.

The subject of nutrition in pregnancy is a neglected phase of obstetrics. In our dietary survey of some 550 pregnant women we have found that very few women at any economic level ingested a diet which is regarded as optimum for pregnancy.

If the high proportion of selective service rejections for nutritional deficiencies in the men who have been examined is equalled among the women, we may expect an equally high proportion of unfit women trying to bear children. The disasters in this group undoubtedly have a marked influence on our maternal mortality, stillbirth and neonatal death rates.

DR. ROBERT SHOEMAKER.—Our work indicates that the adaption test is relatively worthless; certainly there are more than 6 per cent of women low in vitamin A. Likewise we have not done enough blood studies for these to be considered important. Variations are too great, and we know there are many mistakes.

Hellmann, R.: Concerning the Harmlessness of Pantocain for Spinal Anesthesia With Special Reference to the Circulatory Conditions and the Blood—Cerebral Fluid—Relationship, *Ztschr. f. Geburtsh. u. Gynäk.* 120: 1, 1939.

Pantocain is particularly suitable for spinal anesthesia in gynecologic operations. With the previously used viscotic pantocain "L" two deaths were encountered. In the second series of 600 cases, there was not a single death even though no prophylactic measures were taken to prevent circulatory collapse. There were no failures and the anesthesia lasted over two hours. The author believes that the changes in the cerebral fluid which have been observed by some investigators are of little significance. No toxic symptoms appeared as a result of the pantocain even when this anesthetic was repeated.

A fall in blood pressure during a spinal anesthesia is an indication of beginning vasomotor collapse. In obstetrics spinal anesthesia is used in carrying out the Delmas procedure. The only collapse in the author's series of 600 cases occurred during a cesarean section.

Headaches do not often occur after pantocain, and there were no serious complications.

J. P. GREENHILL.

levels without those skin lesions in nephrosis and chronic nephritis, and in the last instance, high vitamin A level indicating possible loss of liver storage. The placenta appears to be no barrier to carotene, and probably not to vitamin A.

Steininger, Roberts, and Brenner<sup>6</sup> from Chicago University have established long range adult levels from 4 subjects and one control after prolonged depletion laboratory diets, and normal single values among 34 average subjects one-half supplemented with vitamin A and one-half unsupplemented, taking fasting blood samples. They found no correlation between biophotometer and blood tests for vitamin A, but direct relation to depletion diet and supplementary feeding by serum estimations.

Depletion diets caused a maximum drop from 17 to 7.1 blue units, and lowest level in any case, 5 blue units. A mean of 9.4 blue units per 100 c.c. of serum with an average deviation of 2.6 units among 17 unsupplemented average adults and a mean of 15.8 blue units per 100 c.c. with an average deviation of 3.0 units in supplemented cases was established.

Fig. 3 represents severe consistent "night blindness" in one woman during a tenth pregnancy, complicated by long-standing unrefracted cataract in one eye plus pre-eclampsia, as compared to normal dark adaptation during her uncomplicated eleventh pregnancy with corrective glasses. This case demonstrates error in dark adaptation by local ocular pathology, since the toxemia was mild.

#### SUMMARY AND CONCLUSIONS

1. Three hundred and twenty-eight additional pregnant women under good prenatal dietetic management were tested by the Feldman adaptometer for deficient vitamin A; and 34 were tested similarly and by blood serum estimations.

2. The adaptometer indicated only 0.62 per cent deficient in vitamin A, whereas the serum content was abnormal in 40 per cent of single readings as well as uncorrelated.

3. Subjective biophotometric tests for vitamin A are not applicable for determination of the status in pregnancy.

4. Chemical tests of pregnancy blood serum also offer doubtful means of assaying vitamin A capacity in pregnancy.

5. Dietetic insufficiency in pregnancy should be assumed, and artificial vitamin A supplement offered in all cases.

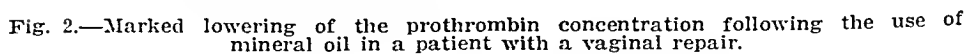
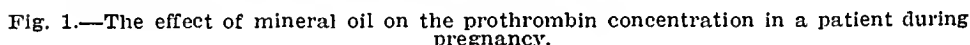
#### REFERENCES

- (1) *Lehman, Edward, and Rapaport, Howard G.*: J. A. M. A. 114: 386, 1940. (2) *Holman, Emile*: Surg., Gynec. & Obst. 70: 261, 1940. (3) *Williams, P. F., Hark, Bernard, and Fralin, F. G.*: AM. J. OBST. & GYNEC. 40: 1, 1940. (4) *Hirst, J. C., and Shoemaker, R. E.*: Ibid. 40: 12, 1940. (5) *Clausen, S. W., and McCoord, A. B.*: J. Pediatr. 13: 635, 1938. (6) *Steininger, G., Roberts, L. J., and Brenner, S.*: J. A. M. A. 113: 2381, 1939.

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#### DISCUSSION

DR. PHILIP F. WILLIAMS.—Some months ago a study was made at the Presbyterian and Jewish Hospital Prenatal Clinics of the vitamin A content in the diets of 123 pregnant women. Simultaneously the dark adaptation time was determined. We found that there was a marked deficiency of vitamin A content in the diet of 62 per cent of the women; and a considerable deficiency in the dark adaptation time of 37½ per cent. We did not find, however, that there was a close relationship between the process of regaining vision in darkness and the intake of vitamin A in the diet.



# PROTHROMBIN CONCENTRATION AND MINERAL OIL\*

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DURING an investigation of the prothrombin concentration† in normal pregnancy, one patient, having a prothrombin concentration of 100 per cent of normal in the twelfth week of gestation, developed an unexplained decrease to 71 per cent. During the following twenty weeks, synthetic vitamin K (Thyloquinone, Squibb) was administered orally, and the prothrombin level did not increase and ranged between 70 and 80 per cent. It was only after intramuscular injections of vitamin K that the prothrombin was raised to 100 per cent in the thirty-second week of gestation (see Fig. 1). Thereafter, a second decline occurred to 52 per cent, despite the fact that the patient was eating an adequate diet, was gaining weight properly, and was taking vitamin K orally. Finally, close interrogation disclosed the fact that the patient had taken mineral oil at intervals since the thirteenth week of gestation without our knowledge. On discontinuing the oil, and continuing the oral and intramuscular administration of K, the prothrombin level was maintained at 100 per cent up to term, during labor and the puerperium. In this regard, the cord blood prothrombin is of interest, as it was only 33 per cent of normal, which is not a significant increase, despite the large amount of vitamin K given to the mother before and during labor.

Mineral oil is commonly used by many either intermittently, two or three times a week, or regularly at daily intervals; therefore, several patients were studied under both conditions. The results are tabulated in Table I.

As shown in the table, intermittent use of mineral oil reduced the prothrombin levels in 3 out of 9 patients (33 per cent); while daily intake

TABLE I. PROTHROMBIN CONCENTRATION AND MINERAL OIL

CASES	OIL INTERMITTENTLY	PROTHROMBIN CONCENTRATION PER CENT	CASES	OIL DAILY	PROTHROMBIN CONCENTRATION PER CENT
1. O.C.	15 c.c. b.i.w.	100	1. G.	30 c.c. t.i.d.	81
2. S.	15 c.c. t.i.w.	100	2. B.	30 c.c. b.i.d.	69
3. A.	15 c.c. b.i.w.	100	3. D'A.	30 c.c. b.i.d.	23
4. H.	20 c.c. t.i.w.	100	4. G.	15 c.c. b.i.d.	52
5. G.	15 c.c. t.i.w.	100	5. E.	15 c.c. t.i.d.	100
6. A.	30 c.c. t.i.w.	100	6. C.	30 c.c. b.i.d.	100
7. P.	15 c.c. t.i.w.	33	7. S.	30 c.c. t.i.d.	69
8. G.	15 c.c. t.i.w.	69	8. C.	15 c.c. t.i.d.	100
9. C.	15 c.c. t.i.w.	61	9. J.	30 c.c. t.i.d.	33
			10. J.	30 c.c. t.i.d.	61

\*Submitted for publication, June 4, 1941.

†The Warner, Brinkhaus and Smith technique was used for the Prothrombin determinations under a grant from the John and Mary R. Markle Foundation through the courtesy of Dr. William DeWitt Andrus.

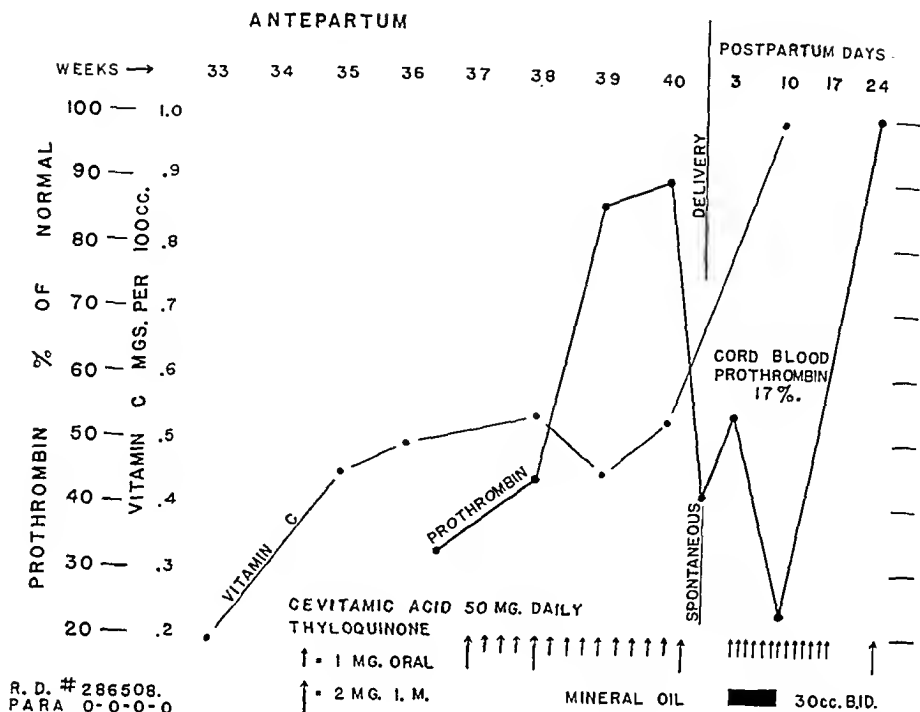


Fig. 3.—Hypoprothrombinemia during pregnancy, corrected by the administration of vitamin K; its recurrence following parturition and further decrease after mineral oil was given daily with vitamin K.

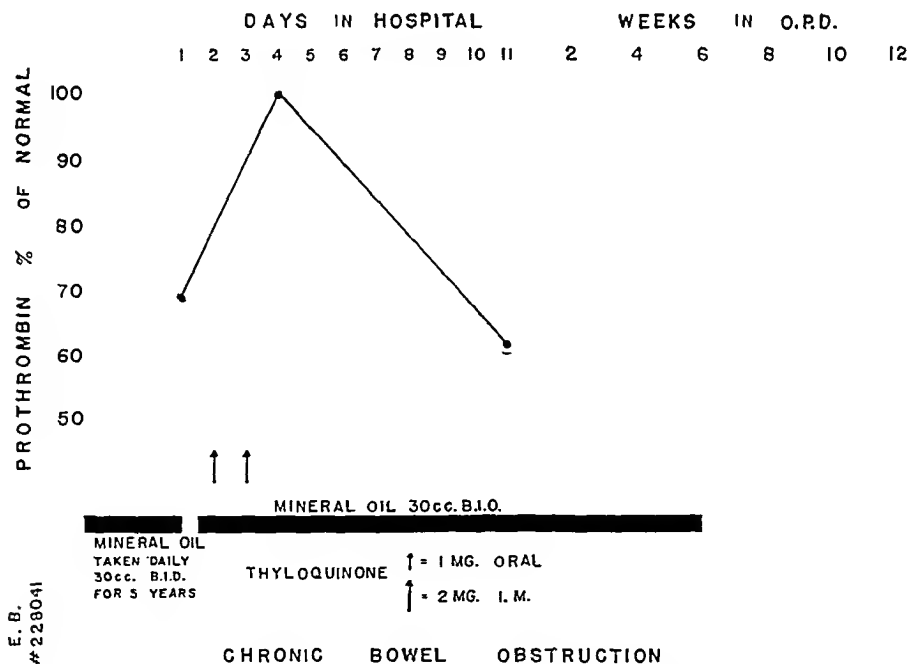


Fig. 4.—Hypoprothrombinemia in a patient with a chronic bowel obstruction in whom parenteral administration of vitamin K produced a normal prothrombin concentration.

of the oil for one or two weeks or longer, resulted in a lowered prothrombin in 7 out of 10 patients (70 per cent). Apparently, mineral oil interferes with absorption by adsorption of vitamin K, or by inhibiting bacterial synthesis in the intestine. The oil may even accumulate in the liver cells. Whatever the mode of action, the evidence suggests the occurrence of hypoprothrombinemia in certain patients following the oral ingestion of mineral oil. In order to prove or disprove this contention, a more systematic study was made on a number of pregnant and non-pregnant individuals.

The prothrombin curve of a gynecologic patient, on whom an anterior and posterior repair was performed, under local anesthesia, is shown in Fig. 2. She was given mineral oil for eight days, with a reduction in the prothrombin level from an initial value of 100 per cent to 68 per cent. A further drop to 33 per cent occurred even after the oil had been discontinued for another eight-day period. Thereafter, a gradual increase occurred without the administration of synthetic vitamin K. This patient had an uncomplicated postoperative course, and an adequate diet was maintained throughout.

An obstetric patient was studied next, since her prothrombin concentration was 33 per cent of normal in the thirty-sixth week of gestation. The administration of thyloquinone orally and parenterally produced a rise to 90 per cent at term. Delivery was spontaneous after a twenty-eight-hour labor, and at this time the prothrombin level was 41 per cent despite the fact that 2 mg. of thyloquinone was given during labor. The prothrombin was 54 per cent on the third post-partum day. At this time, mineral oil was prescribed as shown in Fig. 3, and 1 mg. of thyloquinone was given daily with bile salts. Nevertheless, the prothrombin decreased to a critical level of 23 per cent; therefore, the oil was discontinued. The vitamin K was continued, and ultimately the prothrombin level was 100 per cent. The cord blood prothrombin was 17 per cent of normal despite the administration of vitamin K to the mother, and it appears that if the mother is deficient, she will retain the vitamin K for her own needs and that little reaches the child. Incidentally, this patient also had avitaminosis C, and we have seen such an association in a number of other patients. Fifty milligrams of cevitamic acid were given daily without a satisfactory rise antenatally, indicating that the dosage should have been greater.

The record of a patient with chronic bowel obstruction (following five laparotomies), for which mineral oil has been taken daily, is shown in Fig. 4. The initial prothrombin was 68 per cent of normal, and the intramuscular administration of 4 mg. of thyloquinone produced an elevation to 100 per cent. During this time, it was necessary to continue the mineral oil, and in a week's time, the prothrombin had decreased to its original level. The hypoprothrombinemia was corrected by the parenteral administration of vitamin K, indicating that even if the oil accumulated in the liver, the production of prothrombin is not interfered with. We have observed several other patients with a prothrombin concentration of around 70 per cent of normal when mineral oil had been taken daily over long periods of time.



of other fat-soluble vitamins, i.e., D and E. In any event, the use of mineral oil may not be the innocuous habit that its ease in administration has caused it to become.

After our observations had been made, it was learned that Elliott, Isaacs, and Ivy had produced prothrombin deficiency with mineral oil in rats on an adequate diet. They stated that there was insufficient evidence to conclude that oil interfered with absorption of vitamin K. They doubted that the oil produced liver injury.

### CONCLUSIONS

1. A lowering of the prothrombin concentration was observed in a patient taking mineral oil without our knowledge, and was responsible for our ultimate discovery of a probable relationship.

2. Oral ingestion of mineral oil in daily doses was associated with lowered prothrombin values in 70 per cent of the patients, while intermittent use of the oil resulted in hypoprothrombinemia in 33 per cent of the cases.

3. The prothrombin concentration in patients receiving oil daily was often reduced to lower levels than when oil was used intermittently.

Occasionally, small doses of oil failed to lower the prothrombin level of patients having had an adequate diet. Whether larger doses will do so awaits further investigation.

4. The role of mineral oil in producing hypoprothrombinemia is probably by prevention of absorption of vitamin K, or by adsorption of the vitamin by the oil, or by interfering with bacterial synthesis. The accumulation of the oil in the liver parenchyma is also probable but does not prevent utilization of vitamin K administered parenterally as shown by one case.

5. From the evidence at hand, the oral administration of vitamin K to pregnant women may prove of little or no value unless the simultaneous use of mineral oil is curtailed.

6. The effect of interdicting the maternal use of mineral oil on the incidence of hemorrhagic disease of the newborn is awaited with interest.

The thyloquinone was supplied by E. R. Squibb & Co.

### REFERENCES

- Elliott, M. C., Isaacs, B., and Ivy, A. C.: *Proc. Soc. Exper. Biol. & Med.* 43: 240, 1940. Rowntree, J. I.: *J. Nutrit.* 3: 345, 1931. Warner, E. D., Brinkhous, K. M., and Smith, H. P.: *Am. J. Physiol.* 114: 667, 1935-1936.

Another patient was seen in the twenty-eighth week of gestation with a prothrombin concentration of 42 per cent of normal. Mineral oil had been taken for years. The prothrombin was increased to 81 per cent by withdrawal of the oil and correcting the diet so that spinach, watercress, and lettuce were included. Of interest is the fact that in 1938 this patient sustained a post-partum hemorrhage for which a transfusion was given. Thyloquinone, 1 mg. daily, was given orally

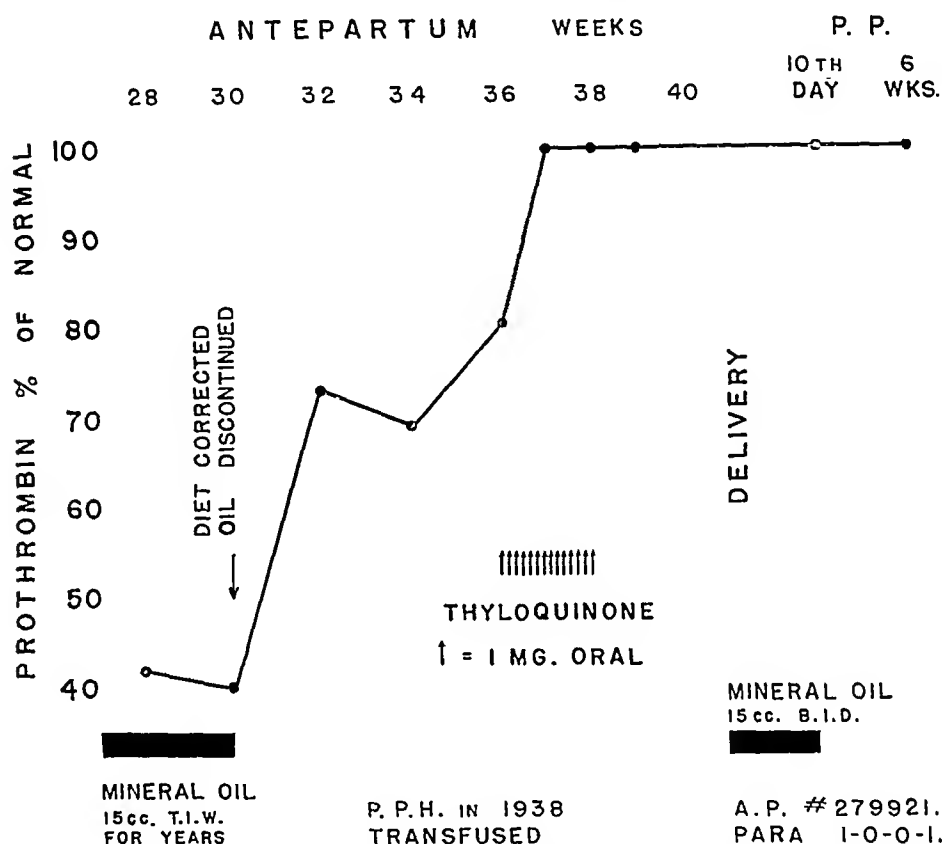


Fig. 5.—Showing an increase in the prothrombin concentration following dietary correction and discontinuance of mineral oil.

for two weeks during which time the prothrombin concentration was maintained at 100 per cent of normal (Fig. 5). Delivery was spontaneous with a blood loss of 200 c.c. Mineral oil, 15 c.c. b.i.d., was given for a short period post partum (ten days) without a drop in the prothrombin concentration. Occasionally, small amounts of oil failed to lower the prothrombin level in patients having had an adequate intake of vitamin K prior to the administration of the oil.

Mineral oil is frequently prescribed for pregnant patients, and since it appears to induce hypoprothrombinemia in certain patients, the routine administration of vitamin K in pregnancy under such circumstances may prove unsuccessful. This is of practical application in the treatment of maternal deficiency as well as in the reduction of the incidence of hemorrhagic disease of the newborn. The oil also interferes with the absorption of carotene, the precursor of vitamin A, according to Rowntree and others. It is possible that it prevents the metabolism

ward so that at the beginning of the second trimester of pregnancy, the prothrombin level is 94 per cent of normal. However, a distinct lowering occurs at the end of the second trimester. This may be due to requirements of the fetus. On the other hand, the patients may have been advised to take mineral oil, which the authors have shown elsewhere produces significant lowering of the prothrombin concentration in certain patients. In the last trimester, a gradual increase takes place again, so that at term the average prothrombin level has reached 95 per cent of normal.

At the time of delivery, there is a decrease in the prothrombin concentration, although only 14 per cent of the patients studied at this time were below 70 per cent. These patients would probably have profited by the administration of vitamin K either just prior to, or during, parturition in order to improve their deficiency. The administration of vitamin K under such circumstances would probably not benefit the child since the prothrombin concentration of the cord blood

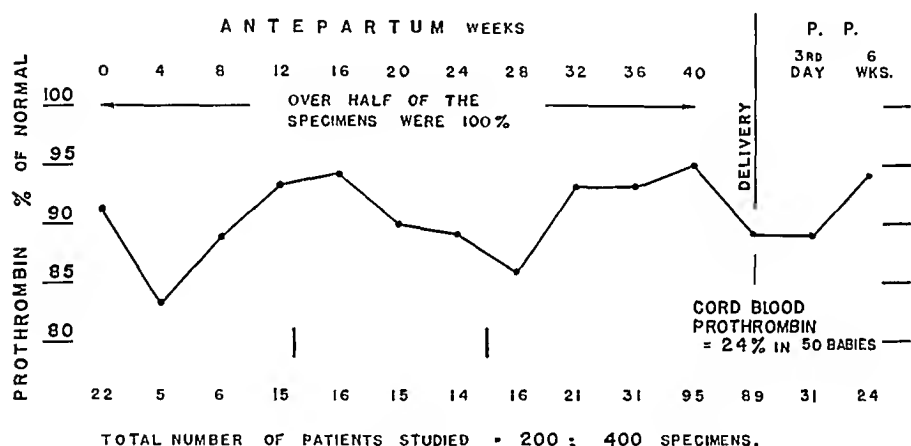


Fig. 1.—Plasma prothrombin concentration in normal pregnancy.

has not been elevated under such circumstances as shown by a number of our cases. This suggests that the mother retains the K for her own requirements and that little or none of the vitamin reaches the infant, or the fetus is unable to utilize it.

The drop in the prothrombin at delivery, shown in Fig. 1, is maintained on the third day post partum and is probably due to a lowered intake of K or to faulty digestion and metabolism during labor. On the other hand, there may be an increased destruction of prothrombin in the lungs. The work of labor was thought to be a factor but this view was discarded on the following evidence:

Five normal subjects, 3 with a prothrombin concentration of 100 per cent, and two with levels of 61 and 68 per cent of normal, respectively, rode a bicycle or played squash for an hour. Immediately thereafter, the prothrombin studies were repeated and no significant decrease was observed in any of the five subjects.

It appears that exercise (i.e., labor) does not lower the prothrombin concentration, indicating that other factors are responsible, i.e., lowered dietary intake and faulty digestion as the patient approaches labor.

## PROTHROMBIN CONCENTRATION IN NORMAL PREGNANCY\*

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THE prothrombin concentration of blood plasma has been shown repeatedly in the literature to be related to the intake of vitamin K and to proper liver function. There is a paucity of information regarding the maternal prothrombin values although pregnant patients have been studied by many investigators with regard to reduction of the incidence of hemorrhagic disease of the newborn by ante-partum or parturitional administration of vitamin K. A knowledge of the prothrombin concentration in pregnancy is extremely important in order to determine the incidence of vitamin K deficiency and also to verify or refute the rationale of administering vitamin K to every pregnant patient.

In order to clarify this situation somewhat, the prothrombin concentration of 200 normal pregnant women was determined. At times significant variations were observed, but in general, the majority of the patients showed a normal prothrombin concentration indicating adequate intake and utilization of vitamin K.

The Warner, Brinkhous, and Smith technique was used for the prothrombin determinations.† The 200 normal patients were studied at various intervals during the antenatal period and again in labor and in the puerperium. Of the total number, 15 had values determined at monthly intervals, but since no significant variation was observed, all of the data were combined and average values were obtained, and these are presented in Fig. 1. Of importance in interpreting this curve is the fact that 225 of the 400 determinations comprising it were 100 per cent of normal. Of the 200 patients studied, 170, or 85 per cent, showed a concentration between 71 and 100 per cent, and 30, or 15 per cent, were 70 per cent or below. Many in the latter group were given synthetic vitamin K either orally or by intramuscular injection with elevation in the prothrombin values often to 100 per cent and, therefore, were considered to have hypovitaminosis K on a nutritional or metabolic basis in the absence of liver disease.

As shown in Fig. 1, the primary trend of the prothrombin concentration is upward during pregnancy, with the highest value occurring at term. Secondary trends are apparent when the curve is studied from the standpoint of the trimesters of pregnancy. In early pregnancy, the prothrombin concentration is lowest, probably due to a lowered intake of foods containing vitamin K because of "morning sickness" and its attendant nausea and vomiting. Thereafter, the secondary trend is up-

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†These determinations were made possible under a grant from the John and Mary R. Markle Foundation through the courtesy of Dr. William DeWitt Andrus.

TABLE I. THE PARENTERAL INJECTION OF SYNTHETIC VITAMIN K IN THE NEWBORN

NO. INFANTS TREATED	PREPARATION USED	NO. OF REACTIONS	ABSCESS FORMATION	INFANTS HAVING HEMORRHAGIC DISEASE
196	Thyloquinone, 2 mg. in corn oil	98	1	0
360	Thylohydroquinone, 1 mg. in aqueous solution	29	1	0
Total 556				0

ordinarily, five should have done so, since the clinic incidence of this disease is 0.77 per cent. These studies are being continued at the present time in order to have a larger series of cases. From the evidence at hand, parenteral injection of synthetic vitamin K in the newborn may prevent hemorrhagic disease more effectively than does the maternal administration of the vitamin.

#### CONCLUSIONS

1. The composite curve of prothrombin concentration was determined in normal pregnancy and the primary trend was upward, with secondary trends having the lowest level in the fourth week, probably due to dietary disturbance caused by morning sickness; while the next low level seen in the twenty-eighth week was probably due to fetal requirements of K.

2. The prothrombin concentration was 70 per cent or below in 15 per cent of 200 normal pregnant women; therefore, they were regarded as having hypovitaminosis K.

3. The cord blood prothrombin concentration at delivery was 24 per cent of normal, while the mothers had a level of 89 per cent of normal. This indicates that prothrombin molecule does not traverse the placental barrier.

4. At term and at the time of delivery, 14 per cent of the mothers were below 70 per cent, and they would have profited by the administration of vitamin K. Studies have indicated that under such circumstances, the mother evidently retains the K for her own needs and that very little if any reaches the fetus, or the child is unable to utilize it.

5. It is probable that the fetal liver cannot utilize K for the production of prothrombin because of the patent ductus venosus. It is only after ligation of the cord that the prothrombin level rises in the newborn infant.

6. Parenteral injections of synthetic vitamin K given to the infant at delivery seem indicated because of the universal hypoprothrombinemia at birth and the early onset of hemorrhage disease of the newborn. Five hundred and fifty-six infants were given synthetic vitamin K at delivery, and hemorrhagic disease did not develop in any of these infants. Under average circumstances, 5 infants should have had the disease. An additional series of cases are being studied for confirmation of this view.

7. The maternal prothrombin level in the puerperium showed no significant deviation due to lactation.

Thyloquinone was provided by E. R. Squibb & Co.

During the puerperium, there was no further decrease in the prothrombin due to lactation, since the values were essentially normal at six weeks postpartum.

At the time of delivery, the cord blood of 50 infants showed an average concentration of only 24 per cent of the adult normal. This indicates that the placenta is a barrier to the passage of prothrombin. According to numerous papers in the recent literature, vitamin K administered to the mother produces significant rise in the prothrombin levels of the cord blood. This treatment has been seized upon with regard to prevention of hemorrhagic disease of the newborn. However, if the mothers are deficient (and about 15 per cent seem to be), such treatment would benefit these mothers, which is not a bad idea, but our experience teaches that under such circumstances very little improvement can be expected in the prothrombin concentration of the cord blood. Naumenec, Hellman, and Shettles have recently come to the conclusion that K given during labor does not raise the baby's prothrombin. Originally they were among the first to advocate the use of K in labor.

The marked hypoprothrombinemia of the infant at birth is in itself an indication for the parenteral administration of vitamin K, not to mention the early onset of hemorrhagic disease of the newborn. Javert has reported three cases in which the intrauterine onset of hemorrhagic disease of the newborn was well substantiated. He has also shown further that the disease often occurs on the first day of life. These facts go well hand in hand with the physiologic hypoprothrombinemia (deranged clotting mechanism) of the cord blood and the trauma of labor (capillary rhexis) as etiologic factors in the causation of hemorrhagic disease which calls for parenteral injection of vitamin K to the infant at the time of delivery, as has been suggested by Javert in a discussion of vitamins and pregnancy. It is very probable that parenteral injection of K will become as routine as is the instillation of silver nitrate into the conjunctival sac, and perhaps with greater justification.

There is considerable doubt that the liver of the child is able to metabolize vitamin K during intrauterine life, as suggested by the marked hypoprothrombinemia of the cord blood. It is quite possible that the patent ductus venosus shunts blood around the liver and thereby contributes to liver deficiency as first suggested by Javert and Moore. If this assumption is correct, only when the cord is ligated will the liver begin to function normally with the production of prothrombin so the concentration rises after a few days after an initial drop, as has been observed clinically. To facilitate the formation of prothrombin by the infant, parenteral injection of vitamin K seems indicated immediately after delivery rather than during labor. The practicability of such a procedure was studied in 549 infants as shown in Table I.

In the first series, thyloquinone in corn oil produced local induration at the site of injection in 50 per cent of the infants, and this was invariably absent on the day of discharge from the hospital. When thylohydroquinone was employed, only 11.4 per cent of the infants showed localized reaction, and these cleared up in a few days. Each solution resulted in one abscess which was probably of technical origin. It is of interest that no infant developed hemorrhagic disease of the newborn;

In 1924 Stevens and Arthurs<sup>6</sup> reported a group of 105 pregnant women in which 33 per cent had residual urine. Of 36 patients catheterized on the second day post partum, 29 had residual urine. They believe that trauma and reflex nerve disturbances associated with lowered abdominal pressure result in partial urinary retention immediately post partum.

Textbooks on urology avoid the subject entirely with the exception of Young's *Urology*, where Stevens' article is quoted.

With this information at hand a study of the post-partum bladder was undertaken from a standpoint of its cystoscopic appearance and also the intravesical pressure as measured by the cystometer at various levels of bladder capacity.

An effort was made to select a cross section of the patients delivered on the Obstetrical Service of the Los Angeles County General Hospital. All patients delivered from midnight Monday to midnight Tuesday each week were sent to cystoscopic clinic on Thursday morning of that week. The only patients excepted were those delivered by cesarean section. There were 105 patients examined in the first group. Of these

42	were para i
25	were para ii
18	were para iii
7	were para iv
6	were para v
2	were para vi
3	were para vii
1	was para ix
1	was para xii

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105

All cases were examined from thirty-six to sixty hours after delivery with an average of forty-eight hours. The age range was fourteen to thirty-six years, with an average age of 23.7 years. The different methods of delivery were divided as follows:

52	were delivered spontaneously without episiotomy
21	were delivered spontaneously with episiotomy
31	were delivered by low forceps with episiotomy
1	breech six-months' fetus after use of bag

Following the examination and observation of the 105 cases, there were 11 operative cases selected as follows for examination:

7	Breech deliveries
2	Midforceps
1	Podalic version and extraction
1	Low cervical cesarean section

Some difficulty was encountered in securing a larger number of mid-forceps, and in addition most cesarean section cases have indwelling catheter drainage from forty-eight to seventy-two hours routinely.

Baby weights varied from the largest, 10 pounds 5 ounces, to two prematures. The average infant weight was 7 pounds 4 ounces. There was one twin pregnancy.

## REFERENCES

- Javert, C. T.: AM. J. OBST. & GYNEC. 40: 453, 1940. *Idem*: Ibid. 35: 200, 1938. *Idem*: Vitamins and Pregnancy, Clinics of North America, Philadelphia, May, 1941, W. B. Saunders Co. Javert, C. T., and Macri, C.: AM. J. OBST. & GYNEC. 42: 415, 1941. Javert, C. T., and Moore, R. A.: AM. J. OBST. & GYNEC. 40: 1022, 1940. Naumenee, A. E., Hellman, L. M., and Shettles, L. B.: Bull. Johns Hopkins Hosp. 68: 158, 1941.
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## STUDIES OF THE POST-PARTUM BLADDER

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MEDICAL literature contains very little information concerning the post-partum bladder. This fact is unusual in the light of the tremendous volume of literature on all other parts of the urinary tract in the various periods of pregnancy and the puerperium. Reports and observations dealing with this subject are limited to a few short paragraphs or incidental findings included as a part of a discussion of the urinary tract as a whole.

Most textbooks in obstetrics pass over the subject with generalities about a lack of desire to empty the bladder and with vague descriptions of the trauma to the bladder and urethra incurred during labor.

Stander,<sup>1</sup> in *Williams Obstetrics* where the most complete discussion is found, states that the process of evacuation of the uterus is associated with stretching and trauma of the base of the bladder. Cystoscopic examination after delivery shows not only edema and hyperemia but frequently submucosal hemorrhages.

At times the edema is so marked as to cause obstruction and retention.

The post-partum bladder has an increased capacity and is not so sensitive to intravesical fluid tension. Overdistention is, therefore, common with residual urine. The paralyzing effect of anesthesia and temporarily disturbed function of the nerve supply to the bladder undoubtedly are contributory factors.

In 1906 Holtze<sup>2</sup> found an average of 107 c.c. of bladder residual urine in primiparas post partum and 58 c.c. in multiparas post partum. These all returned to normal within one week.

Stuernagel,<sup>3</sup> in 1912, found that bladder capacity was increased post partum in many cases to a point at which the desire to void did not occur before 1000 c.c. of retention, and it was not unusual for 2,000 c.c. to be tolerated.

In 1921 Walker<sup>4</sup> used a mercury manometer to measure bladder pressure in the male and included in his report the observation "that several puerperal women examined showed evidence of decreased pressure." In 1922 Shutter<sup>5</sup> found that in a small group of nonpregnant women the desire to void occurred at 200 c.c. (this was increased to 350 c.c. at term in the pregnant), but that 800 c.c. produced only slight feeling of pressure post partum. He investigated several patients post partum, using a mercury manometer which showed very low pressure of from 2 to 6 mm. of mercury.



floor, and trigon. This was associated with some distortion of the trigon and floor caused by pressure and protrusion of the enlarged cervix and uterus, the picture being generally that of a congested atonic bladder. Mucosal edema was present in varying degrees but in no cases was it sufficiently marked to be an obstructive factor. In only 19 cases of the entire 116 (of both the original 105 and the selected operatives) were there any evidences of ecchymosis, such as might be expected from direct trauma. In 14 cases the areas of ecchymoses were limited largely to small areas about one or both ureteral orifices. In the remaining 5 cases the ecchymosis involved the greater part of the trigon and base.

Of the 14 patients, 6 were delivered spontaneously with episiotomy and 4 without. Two patients were delivered by low forceps and 2 were breech deliveries. The 2 patients delivered as breeches had very small punctate areas of hemorrhage.

The 5 patients with more or less extensive ecchymosis were delivered, 3 as spontaneous and 2 as low forceps.

The duration of labor in the group showing ecchymosis averaged fifteen hours, fifty-four minutes for the first stage; forty minutes for the second stage; twelve minutes for the third stage. There was only one patient of this group that had a protracted labor, that of fifty-six hours. This comparison does not account for the obvious trauma of the bladder on a basis of length of labor or by difference between spontaneous and operative delivery.

In cystoscopy examination of the 7 breech deliveries, the bladder had the general appearance of that observed in the other cases.

Observation of the bladder in the case of the low cervical cesarean section showed no evidence of ecchymosis. The muscular tone, however, was good. This patient had an indwelling catheter during the first forty-eight hours post-partum.

Indigoearmin dye appeared from the ureteral orifices in an average of five to six minutes after intravenous injection. In 6 cases appearance was delayed from one or the other ureteral orifice more than ten minutes, and in 3 cases no dye appeared from the right ureteral orifice in fifteen minutes.

*Other Pathology.*—Unilateral duplication of ureteral orifices was noted in two cases and in one case the left ureteral orifice and left ureteral ridges were absent entirely.

#### CYSTOMETRIC FINDINGS

The normal bladder responds to distention in a characteristic manner. A cystometrogram or a chart recording intravesical pressures, as recorded by a manometer at various degrees of distention, presents a fairly accurate picture of the functional state of the bladder muscle. A normal response is well represented by the following figure which Muschat and others<sup>8</sup> designate as a normal cystometrogram (Fig. 1). Fig. 2 represents a characteristic cystometrogram obtained in the hypertonic group. Fig. 3 represents a characteristic cystometrogram obtained in the atonic or hypotonic group. Fig. 4 represents a composite cystometrogram of this entire series, representing mean average readings of all cases. This shows a definite hypotonic type of curve.

The 105 cases could roughly be divided up into three general groups:

1. Those patients developing painful desire with some bladder spasm before 750 c.c. distention capacity was reached, of whom there were 15.

Duration of labor in stages varies as follows:

First stage, longest 60 hours, shortest 1 hour 25 minutes; with an average of 12 hours 14 minutes.

Second stage, longest 9 hours, 24 minutes, shortest 3 minutes; average 48½ minutes.

Third stage, longest 46 minutes, shortest 2 minutes; average 12.2 minutes.

These patients were allowed to go eight hours before being catheterized. However, the order was discretionary and at times the patients were allowed to go longer than eight hours if there was no discomfort or obvious bladder distention. There were 16 of the 105 cases allowed to go beyond 12 hours before voiding. These varied from fifteen and one-half to twenty-four hours. The amount voided varied between 225 c.c. and 1450 c.c., with an average of 732 c.c. The residual varied from 20 c.c. to 1,100 c.c., with an average of 200 c.c. This obviously was poor post-partum technique. However, no great discomfort compelled the nurses to catheterize before that time. Comparison of these 16 cases with the others shows virtually the same cystoscopic and cystometric findings. Following the first voiding, the volume of residual bladder urine was checked by catheter. There were three of the 105 that were unable to void and required the use of the catheter through the second day. The remainder voided spontaneously in from three to twenty-four hours, with an average of nine and one-fourth hours.

The volume of urine passed at first voiding varied from 100 c.c. to 1,450 c.c., with an average of 478 c.c. Accurate data on residual urine were obtained from 94 of the cases examined, not having been recorded in the remaining 8 cases. Of the 94 patients, 34 per cent had a residual urine in excess of 250 c.c. and in 6 patients, or 6 per cent, in excess of 500 c.c.

#### METHOD OF EXAMINATION

The patients were brought to cystoscopy without premedication, and 5 c.c. of indigocarmine solution were administered intravenously. A No. 24 Brown-Buerger cystoscope was introduced without anesthesia to the bladder. Appearance time and concentration of indigocarmine from ureteral orifices was observed. The bladder cavity was then carefully inspected for evidence of trauma, inflammation, edema, and distortion, care being taken to avoid overdistention during this procedure.

Following this a No. 18 French Pezzer type catheter was introduced into the bladder cavity. The catheter in turn was connected to an improvised mercury cystometer and the bladder was then slowly filled with sterile water. Readings of vesical pressure in millimeters of mercury were recorded at 250 c.c., 500 c.c., 750 c.c., and 1000 c.c., respectively, except in those cases where some bladder spasm developed or in cases where the distention of the bladder became too painful. While many of these patients experienced no sensations of pain or fullness with the bladder distended to 1000 c.c., it was deemed inadvisable to distend them further.

There was also recorded the bladder volume at the first desire to void and also at whatever point a painful desire developed. An attempt to secure the maximum voluntary pressure was made. However, the variability of cooperation of the patients made this determination difficult to interpret.

#### CYSTOSCOPIC FINDINGS

Cystoscopic examination of these bladders revealed varying degrees of mucosal congestion and edema, most marked about the bladder neck,

In the second group there were 43 cases, or 40.9 per cent of the total. The average bladder capacity when this slightly painful desire began was 865 c.c., and the average manometer reading was 21 mm. of Hg.

The third group of 47 cases, or 44.8 per cent of the total, had no pain or desire to urinate with the bladder distended to 1000 c.c. The average manometer reading at 1000 c.c. was 14.8 mm. of Hg.

TABLE I. PATIENTS HAVING PAIN OR BLADDER SPASM BEFORE BLADDER DISTENTION HAD REACHED 750 C.C.

	PERCENTAGE OF CASES	AVERAGE MAXIMUM MANOMETER READINGS MM.	AVERAGE BLADDER CAPACITY AT WHICH PAIN OC- CURRED C.C.
Group average	14.3	33	610
Patients delivered spontaneously without episiotomy	23.1	31.7	604
Patients delivered with low forceps and episiotomy	9.7	38.7	633
Patients delivered spontaneously with episiotomy	0	—	—

In Table I are shown the types of delivery that make up the group of cases developing bladder spasm together with the comparison of the manometer readings and bladder capacity of each group. There were 23.1 per cent of the patients delivered spontaneously that make up this group and 9.7 per cent of the patients delivered by low forceps. The manometer readings and the bladder capacity show a close correlation of the two types of delivery in comparison with that of the group as a whole.

There were no cases in which the patient was delivered spontaneously with episiotomy that fell into this group. No reason for this can be given. The fact that only 23 per cent of patients delivered spontaneously without episiotomy approached the average cystometric finding would seem significant. In addition, in this whole group the bladder capacity is increased; bladder pressure diminished.

Table II shows the comparison of the group of cases in which painful desire developed with the type of delivery. There is an increase in the number of patients of the group that was delivered spontaneously with episiotomy over either of the other types of delivery. The average bladder capacity and the manometer reading show a very close correlation. No reason for the increase in the spontaneous group with episiotomy can be given.

TABLE II. PATIENTS HAVING PAINFUL DESIRE TO VOID WITH BLADDER DISTENDED TO 750-1000 C.C.

	PERCENTAGE HAVING PAINFUL DESIRE TO VOID	AVERAGE MAXIMUM MANOMETER READING MM.	BLADDER VOLUME AT WHICH PAINFUL DESIRE OC- CURRED C.C.
Group average	40.9	26.7	866
Patients delivered spontaneously without episiotomy	28.8	23	872
Patients delivered spontaneously with episiotomy	66.6	29	873
Patients delivered with low forceps and episiotomy	41.9	20.6	852

2. Those patients in whom slight painful desire develops but no bladder spasm occurred to 1,000 c.c. distention, of whom there were 43.

3. Those patients in whom no pain or desire to empty the bladder occurred during distention to 1000 c.c., of whom there were 47.

In the first group, there were fifteen cases, or 14.3 per cent of the total. The average bladder capacity was 610 c.c. and average maximum manometer reading was 33 mm. of Hg.

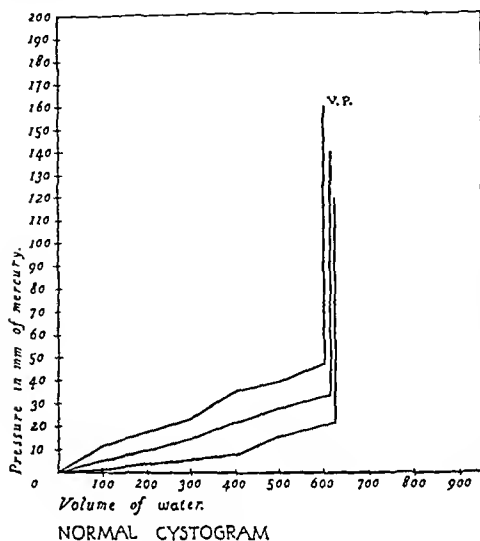


Fig. 1.

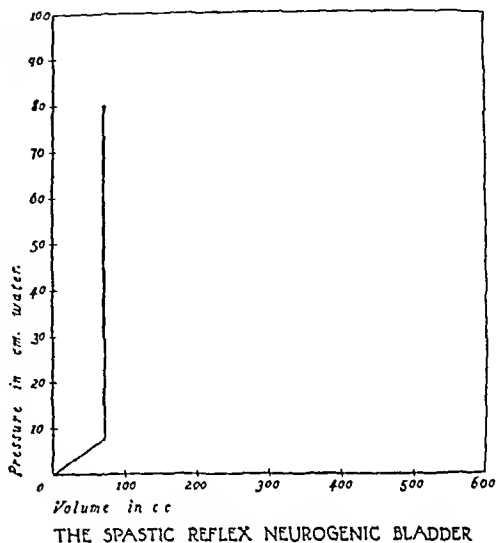


Fig. 2.

Fig. 1.—Cystometric curve, showing maximum, minimum, and average bladder pressures in a group of normal adults, demonstrating gradual increase in pressure up to 600 c.c., then a sharp rise when patient attempts to void.

Fig. 2.—Cystometric curve, showing bladder pressures in spastic neurogenic bladder (compression myelitis). (From McLellan, Frederick C.: *The Neurogenic Bladder*, Charles C Thomas.)

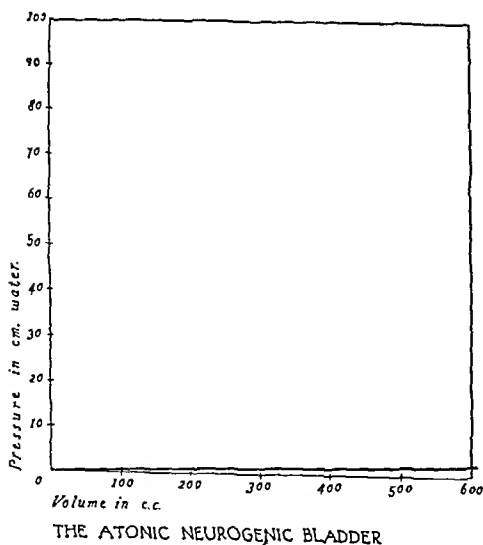


Fig. 3.

Fig. 3.—Cystometric curve, showing bladder pressures in the atonic neurogenic bladder (pernicious anemia). (From McLellan, Frederick C.: *The Neurogenic Bladder*, Charles C Thomas.)

Fig. 4.—Cystometric curve, showing average bladder pressures in the entire group of cases studied. There is a gradual increase in pressure up to 1,000 c.c., then a sharp rise as patient attempts to void. The magnitude of this rise is feeble as compared with the normal.

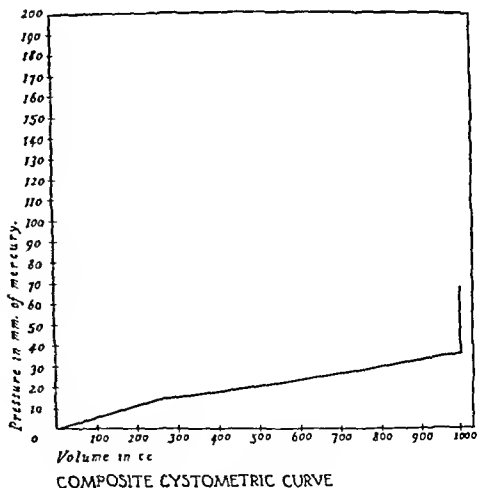


Fig. 4.

## COMMENTS

As seen through the cystoscope, the bladder post partum presents a pale slightly edematous mucosal surface. The bladder wall itself is relaxed and atonic. When deflated it collapses in folds like a paper sack rather than contracting as a normal elastic structure.

Kidney function as evidenced by the use of indigoearmin intravenously in the vast majority of cases falls well within normal limits.

Except for a few cases, mucosal injection, submucosal hemorrhages, and marked edema, such as would be expected from gross trauma, are conspicuous by their absence.

It would be reasonable to assume that bladder trauma would be increased in prolonged labor, in difficult forceps deliveries or in breech deliveries with pressure from above on the aftercoming head. However, a comparison of the 7 breech deliveries with the group of 105 cases originally examined showed no higher incidence of direct bladder trauma. This was also borne out in the two cases of midforceps, the cesarean section and the version and extraction. In the main these patients all come in the same general category, exhibiting little direct bladder trauma. The few cases of this series showing moderately extensive ecchymosis varied very little in their functional response from those showing none. Trauma does not seem to account for the dysfunction of the bladder.

Cystometrograms portray graphically with fair accuracy the functional state of the bladder muscle. Bladder disturbances as pictured by the cystometrogram may be divided roughly into two main groups, the hypertonic or spastic type with increased muscle tone and increased capacity. Each of these groups may be on the basis of myogenic or neurogenic disturbances.

As a group, the post-partum bladder falls into the hypotonic group with decreased bladder sensation, reduced muscle tone and increased capacity. Further comparison of the 105 routine cases with the selected operative case cystometrically shows a surprising similarity of response to distention of the bladder with water. The patient delivered by version and extraction and the two patients delivered by mid-forceps show the same lack of bladder tone. The low cervical cesarean section after two days of bladder rest with an indwelling catheter showed spasm at 650 c.c. capacity and a much better bladder tone.

The anatomical site and nature of this disturbance is not explained. Whether it is primarily neurogenic or myogenic in origin is not known. The fact, however, that past studies have shown this disturbance to be only temporary in nature would indicate that no permanent changes have occurred in either muscle or nerve tissue.

It would seem reasonable in the light of the above findings that post-partum management of the bladder should be directed at alleviating prolonged overdistention and avoiding the ever present threat of urinary stasis. We perhaps should become more bladder conscious of our post-partum cases. It is not inconceivable that prolonged overdistention

In Table III is shown a comparison of the group of patients without pain or desire to void at 1,000 c.c. of bladder distention and the type of delivery. The close relationship between the percentage of the cases of each type of delivery with that of the percentage of the group as a whole is noteworthy. The manometer readings at 1,000 c.c. fall well within the range of that found in the atonic bladder.

Table IV shows the comparison of the general average with that of the 7 breech deliveries.

NO PAIN	SLIGHT PAIN	
57 per cent at 1,000 c.c.	29 per cent at 962 c.c.	14 per cent spasm at 650 c.c.

The two patients with midforceps delivery both had pain at 900 and 950 c.c.; however, both were taken to 1,000 c.c. where the manometer readings were 16 and 11 mm. of mercury, respectively.

There were 20 patients of the 105 that received a light ether anesthetic at the time of delivery but no ante-partum analgesia. The remainder received nembutal and scopolamine in varying amounts from 3 to 7½ ss. gr. of nembutal and one to two doses of 1/150 gr. of scopolamine.

Table V shows a comparison of these two groups and the percentage of the bladder type in each. They both come within close range of the general average for the whole group.

TABLE III. PATIENTS HAVING NO PAIN WITH BLADDER DISTENDED TO 1000 C.C.

	PERCENTAGE HAVING NO PAIN	MAXIMUM AVERAGE MANOMETER READING MM.
Group average	44.8	14.8
Patients delivered spontaneously without episiotomy	48.1	15.6
Patients delivered spontaneously with episiotomy	38.0	13.6
Patients delivered with low forceps and episiotomy	45.1	13.4

TABLE IV. PATIENTS HAVING NO ANALGESIA BUT LIGHT ETHER ANESTHESIA

	NUMBER OF CASES	PERCENTAGE OF CASES HAVING NO PAINFUL DESIRE UP TO 1000 C.C.	PERCENTAGE OF CASES HAVING PAINFUL DESIRE 750- 1000 C.C.	PERCENTAGE OF CASES HAVING PAIN OR SPASM BELOW 750 C.C.
Patients having light anesthesia but no analgesia	20	55	40	5
Group	105	44.8	41	14.2

TABLE V. COMPARISON OF SELECTED GROUP OF ELEVEN BREECH AND OPERATIVE DELIVERIES WITH THE GROUP OF 105 ROUTINE DELIVERIES

	TOTAL NUMBER OF CASES	PERCENTAGE HAVING NO PAIN AT 1000 C.C.	PERCENTAGE HAVING PAIN AT 750-1000 C.C.	PERCENTAGE HAVING PAIN AT 750 C.C. OR LESS
Group of routine deliveries	105	44.8	41.0	14.2
Group of breech and operative deliveries	11	45.5	36.3	18.2

## PLACENTAL BLOOD PLASMA

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THE therapeutic value of adult blood plasma is well established. However, the difficulty in securing blood in sufficient quantities in many hospitals in order that pooled plasma can be safely prepared, particularly where there is no blood bank, stimulated us to investigate placental blood as a source of plasma, and to determine the value of such plasma in clinical use.

Polayes, Lederer and Wiener<sup>1</sup> found in a series of 500 infants, where the Landsteiner blood groups were studied that 283, or 56 per cent, of these infants had no demonstrable specific blood group agglutinins in their serum at birth. Thomsen (cited by Wiener<sup>2</sup>) has shown that in those infants where the blood agglutinins were found to be present they had a very low titer. Because of this lack of specific blood group agglutinins or their very low titer plasma prepared from placenta blood can be considered safer than adult plasma even though small amounts be pooled. This then should be an ideal source of plasma, especially for a small hospital which cannot avail itself of large amounts of adult blood for the preparation of plasma.

We found that sterile plasma can be obtained from placental blood in worth-while quantities. An average of 103 c.c. of whole blood was derived from each placenta, in a series of 200 placentas from which the blood was collected. From 128 c.c. of citrated placental blood, we have obtained an average of 70 c.c. of consistently uncontaminated citrated plasma (25 c.c. of 2.5 per cent sodium citrate solution being placed in each collecting bottle).

Before using placental plasma clinically, we reviewed the literature for comparative analysis of adult and fetal plasma and found that chem-

TABLE I. ANALYSIS OF THE VARIOUS PROTEIN COMPONENTS OF ADULT AND PLACENTAL PLASMA AS DETERMINED BY ELECTROPHORESIS

	FRESH ADULT PLASMA TYPE A (3)* pH 7.72	PLACENTAL PLASMA (21)* pH 7.85
Albumin per cent	3.96	3.47
Albumin/globulin†	2.27	2.00
Alpha globulin albumin	0.08	0.13
Beta globulin albumin	0.18	0.16
Gamma globulin albumin	0.18	0.21
Fibrinogen albumin	0.08	0.05
	Citrated	Oxalated

\*Refers to number in Fig. 1.

†Calculated on serum basis.

post-partum may be a factor in the formation of cystocele in the presence of injury to the bladder base. Further studies will be necessary to determine the exact nature of the dysfunction encountered in these cases.

#### SUMMARY

1. Cystoscopic examination of 116 post-partum bladders revealed general relaxation and minor degrees of mucosal edema.
2. Ecchymosis of bladder mucosa was present to a minor degree in 12 per cent of the cases and to a moderate degree in 4.3 per cent of the cases. This was not increased by breech extraction, nor was it seen in two cases of midforeeps, one case of version and extraction and one low cervical cesarean section.
3. Cystometric studies revealed hypotonic bladders with decreased bladder sensation and increased capacity in 86.2 per cent of the entire series.
4. Type of delivery, trauma, and prepartum analgesia do not account for this dysfunction.
5. A plea is made for attention to the relief of overdistention of the post-partum bladder.

#### REFERENCES

- (1) *Stander*: Williams Obstetrics ed. 7, New York, 1936, D. Appleton-Century Co. (2) *Aerztl. Rund.* 16: 223, 1906. (3) *Ztschr. f. Gynäk. Urol.* 3: 295, 1912. (4) *J. A. M. A.* 77: 286, 1921. (5) *J. A. M. A.* 79: 449, 1922. (6) *J. A. M. A.* 83: 1656, 1924. (7) *Young*: Practice of Urology, ed. 1, Philadelphia, 1926, W. B. Saunders Co. (8) *J. Urol.* 43: 582, 1940.
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Kairis, N. M.: Perisigmoidal Adhesions in Women, *Arch. f. Gynäk.* 168: 84, 1939.

From an analysis of a large series of cases, the author found perisigmoidal adhesions in 20 per cent of all women subjected to laparotomy. These adhesions were most common during the reproductive years and reached their maximum at the age of thirty. These adhesions arise most probably from septic or aseptic inflammatory conditions of the internal genitalia; second, from the sigmoid itself; and third, from the appendix or small bowel. Perisigmoidal adhesions produce no marked symptoms, and there is no definite symptom complex by which the diagnosis can be made. The majority of patients complained of chronic obstipation and irregular pains in the left lower quadrant of the abdomen and these are not characteristic symptoms. In the majority of the cases therefore, no preoperative diagnosis of such adhesions was made. Perisigmoidal adhesions are found most frequently in connection with disease of the left adnexa, with retroversion of the uterus, and with fibroids or adnexal tumors. In many instances, the adhesions are of no clinical significance and when found may be left undisturbed. When they are massive and produce distortion and/or traction, they must be resected. The author insists that during the course of every laparotomy, the pelvis must be carefully examined for such perisigmoidal adhesions. Obviously, resection of such adhesions must be followed by careful and complete peritonization in order to prevent recurrence. Attempt must be made in every instance to restore the sigmoid to its normal position and mobility.

RALPH A. REIS.



As a routine "Seconal"\* is used for analgesia on the obstetric service in this hospital. We felt that the concentration of this drug in placental plasma might contraindicate its use. Therefore a barbituric acid determination was made on Lot 23 which represented 250 c.c. of plasma, pooled from the placentas of 4 patients who had received a total of 1 Gm. of this drug. A concentration of 5.2 mg. per 100 c.c. was found to be present in this 250 c.c. In our experience no hypnotic or sedative effect is produced until the concentration in the blood has reached 20 to 30 mg. per 100 c.c. This laboratory finding confirmed our clinical observation that such a small amount of this barbiturate does not contraindicate the use of pooled placental plasma.

### TECHNIQUE

*Collection.*—The blood is taken from the cord immediately after the birth of the child, prior to the expulsion of the placenta and before any perineal repair is made. The cord is clamped and cut two inches from the umbilicus. A "sterile" assistant immediately cleans it with tincture of "zephiran"† solution 6 to 8 inches proximal to the clamp. The cord is then grasped, compressed with a sterile towel, and severed a short distance from the clamp with another pair of sterile scissors. The "clean" cut end is again cleaned with tincture of "zephiran" solution and inserted into a 225 c.c. graduated, round bottom centrifuge bottle (Fig. 2) into which has been placed, prior to sterilization 25 c.c. of 2.5 per cent sodium citrate solution. The flask and cord are wrapped in the sterile towel and held by the assistant, thus preventing any contamination by amniotic fluid. The cord is then milked to express the blood while pressure is made on the uterus to fill the cord with the blood which remains in the placenta. The flask is covered with a sterile rubber cap to hermetically seal it for transportation. The yield of blood has been greater and the possibility of contamination less when the blood has been obtained prior to the separation of the placenta. This technique is not complicated, and the blood can be collected in a few minutes. A serologic test for syphilis is made on blood obtained from the placenta and the mother after delivery.

*Preparation.*—The blood is placed in a refrigerator at 4 to 6° C. We have obtained a yield which warrants collection by allowing the blood to settle for five or six days and then separating the plasma. However, routinely we centrifuge the blood within twelve to twenty-four hours, and separate the plasma. By this latter technique we have been able to increase the yield of plasma 10 per cent.

By means of an electric suction pump and a 1 c.c. pipette or the special spoon tip suction tube shown in Fig. 2, the clear plasma is removed and pooled in lots of 250 c.c. By decreasing the suction so that a drop at a time can be delivered into the flask, we have found that almost all the plasma can be obtained. When an electric suction pump is not available, a water or hand suction pump can be used satisfactorily. From each 250 c.c. of pooled plasma, 10 c.c., in this series, were taken for culture. To the remainder of the pooled plasma 250 c.c. of 5 per cent glucose in normal salt solution were added, following the advice of Elliott, Busby and Tatum.<sup>5</sup> We have noticed that there is less precipitation in placenta plasma than in adult plasma observed at similar intervals of time after preparation, this being partly due to the lower total fat content of placental plasma. To each 500 c.c. of this diluted plasma, 5 c.c. of a 1 per cent solution of aqueous "merthiolate"‡ are added as a preservative.

Employing the rigid technique outlined, we have not obtained a single positive culture, despite the fact that every 250 c.c. of pooled

\*Seconal—Sodium propyl-methyl-carbinal allyl barbiturate—Lilly.

†Zephiran: Tincture of a mixture of high molecular alkyl-dimethyl-benzyl-ammonium chlorides. Used because of a high germicidal potency and its rapidity of action.<sup>4</sup>

‡Sodium ethyl mercuri thiosalicylate—Lilly.

ieally there is very little difference between the two. Furthermore Scudder<sup>3</sup> has recently pointed out that there is very little difference even in the electrophoretic pattern of the proteins found in adult and placental plasma, and he states that placental blood may be considered a normal

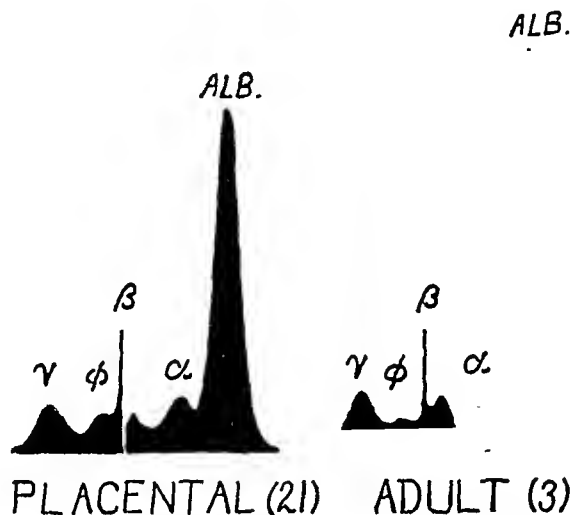


Fig. 1.—The electrophoretic protein patterns of the placental and adult plasma.

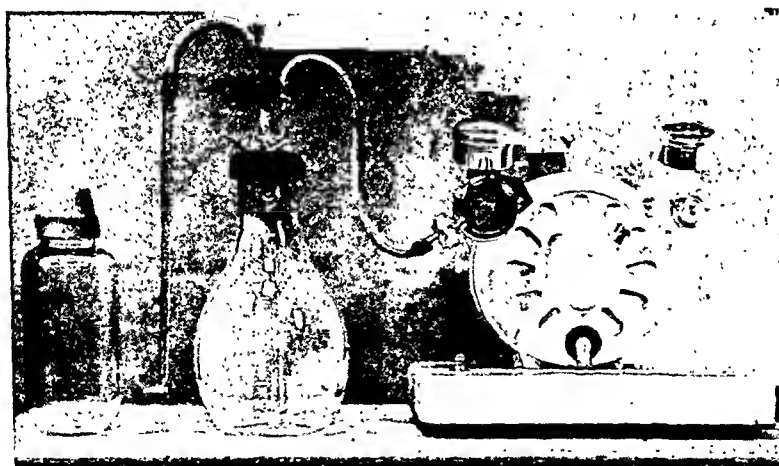


Fig. 2.—The 225 c.c. collecting bottle is shown with the spoon tipped suction tube, bottle into which the plasma is pooled and the electric suction pump. This closed system for pooling the plasma minimizes the possibility of contamination.

source of conserved blood.\* The various protein constituents which make up adult and placental plasma together with their electrophoretic curves are reproduced for comparison with Scudder's permission in Fig. 1 and Table I.

\*Through the courtesy of Longworth of The Rockefeller Institute, we have confirmed the findings of Scudder. Electrophoretic patterns have been made on plasma prepared from the blood of the mother and from placental blood obtained at the time of her delivery, and they show a marked similarity.

marked blood loss. By adding plasma whose coagulating properties have been stated by Goodall, Anderson, Altinas and MacPhail<sup>8</sup> to be 25 to 30 times that of adult blood, we believed that this reduced the amount of blood which the patient lost during the remainder of the operation and postoperatively. This patient made an uneventful recovery and no transfusion of whole blood was necessary. One patient in shock following subtemporal decompression and removal of an epidural hematoma associated with fracture of the skull responded very well to dehydrated placental plasma. This was dissolved in distilled water to four times its normal concentration.

A summary of the case of one patient in shock following an abortion with hemorrhage is given. The dramatic response of this patient to the placental plasma is shown in Fig. 3. In this case as in many of the others where the shock was acute and the shock combating agent urgently needed, the placental plasma bank offered the necessary therapeutic agent.

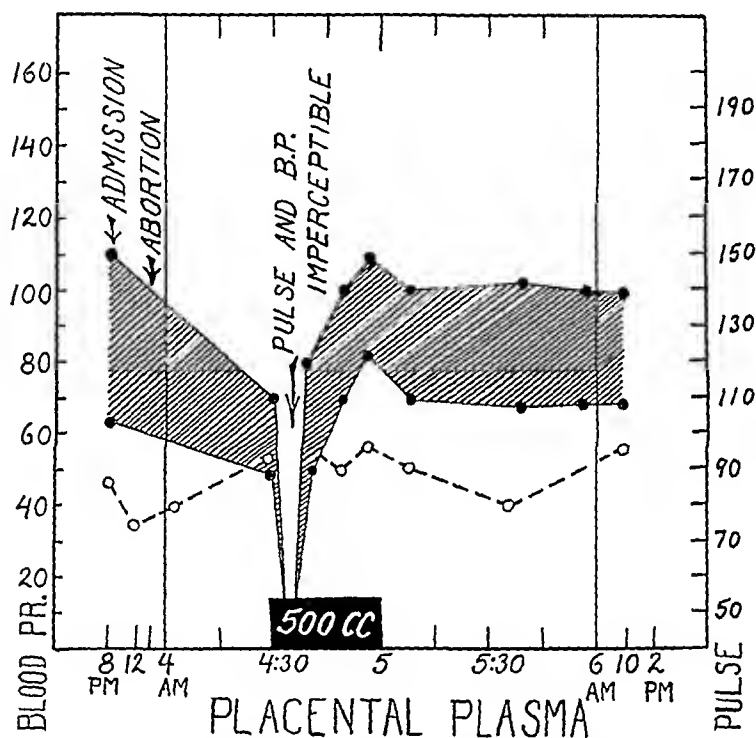


Fig. 3.—(Case 1.) Shock following abortion with hemorrhage, showing effect of placental plasma on pulse rate and blood pressure.

#### CASE REPORT

CASE 1.—E. B., a white female, aged 32 years, multipara, quintigravida, was admitted to the Union Memorial Hospital at 8:15 P.M. on Oct. 23, 1940, with a history of cramp-like lower abdominal pains of four hours' duration. On admission the patient was pale, weak, and complained of abdominal pain and vaginal bleeding. The blood pressure was 110 systolic and 65 diastolic, pulse 86 beats per minute, and the hemoglobin was 11 Gm. The bleeding increased in amount and the abdominal pain became more severe during the next two hours, despite the administration of morphia. Six hours after admission the patient aborted a five months' fetus, but bled profusely before the placenta and membranes could be expressed. Two hours after the abortion the blood pressure dropped to 70 systolic and 48 diastolic, and the pulse at this time was very irregular and hard to count. Ten minutes later the pulse and the blood pressure were imperceptible. At this time 500 c.c. of diluted placental plasma were given intravenously. When 250 c.c. of the plasma had been given, the blood pressure rose to 80 systolic and 50 diastolic while the pulse rate was

plasma has been cultured aerobically and anaerobically before diluting. Aerobically it is cultured on blood agar plates in plain dextrose brain broth\* as well as in dextrose brain broth to which has been added 5 c.c. of whole adult blood. Anaerobically it is cultured on blood agar plates in a carbon dioxide jar.

We have varied the technique of collecting placental blood in several ways. Bacteriologic study shows that blood obtained from the cord without a "cleanup" has given a positive culture, but after employing the technique which we have developed, blood obtained from the same cord has given a negative culture. On the basis of this work we believe the high percentage of positive cultures obtained by Fine, Alter, and Baptisti<sup>6</sup> and Boland, Craig, and Jacobs<sup>7</sup> was due mainly to faulty technique during collection of placental blood. Blood has not been taken from patients in whom the membranes have been ruptured for forty-eight hours or longer nor from those in whom there is any evidence of disease which might be transmitted to the fetus by the mother.

#### CLINICAL USES OF PLACENTAL PLASMA

To date we have used placental plasma in 30 varied clinical conditions. The results have been very gratifying in the clinical response shown and in the complete absence of any local or systemic reactions following its administration.

In four of the patients we used plasma to combat hypoproteinemia. This in two was associated with cardiac failure, in one with carcinoma of the rectum with associated malnutrition, and another in a child, aged 4½ years, with acute glomerulonephritis. In all of the patients there was definite clinical improvement as well as laboratory evidence of an improved plasma protein. The improvement noted in the case of acute glomerulonephritis was most gratifying. For, following the administration of placental plasma, a fall in blood pressure and disappearance of the edema occurred. Prior medical treatment had failed to produce any change.

In four of the cases the placental plasma was given to patients with infections and associated dehydration. The first two were premature infants to whom the diluted plasma was given subcutaneously in doses of 30 to 60 c.c. for two or three days. The clinical response in these two cases was dramatic. The third, a fifteen-day-old infant with an infectious diarrhea received the plasma in the same manner. In these three cases we were able to give subcutaneously a fluid whose electrolyte balance and whose plasma protein were exactly that of the normal infant. The fourth, an adult patient, acutely ill with otitis media and mastoiditis received 800 c.c. of the diluted placenta plasma intravenously and showed definite clinical improvement.

Seventeen of the patients to whom the plasma was given were in shock at the time of administration. The etiology of the shock was due to a variety of causes, such as: incomplete abortion with hemorrhage, operative shock occurring during cesarean section, operative shock during a radical mastectomy, shock associated with first and second degree burns, hemorrhage from a gastric ulcer, hemorrhage from varices of the colon and premature separation of the placenta with concealed hemorrhage. This latter patient who had been treated by the usual routine of morphia and intravenous glucose solution showed signs of improvement which lasted for only a short while. The patient again showed signs of shock just prior to and during a cesarean section. As there was not time to procure a donor for a whole blood transfusion, 500 c.c. of pooled placental plasma were given. This effectively combated the shock, despite the fact that laboratory evidence revealed the patient had sustained a

\*Dextrose brain broth.

1 calf brain  
Delfco nutrient broth  
Sodium chloride  
Dextrose  
Andrade's indicator  
Distilled water

8 Gm.  
8 Gm.  
2 Gm.  
7 c.c.  
1,000 c.c.

3. Chemically and physiologically there are no objections to the use of placental plasma.

4. Placental plasma can be administered after the usual methods of preservation to patients on a diversity of indications with absolute safety, without local or systemic reaction.

5. Clinically, placental plasma is equal in therapeutic value to adult plasma, and its general use may prove to be more satisfactory.

6. With very little effort any hospital with or without a blood bank but with a maternity service can prepare blood plasma for clinical use.

7. In the time of a National emergency, military or otherwise, placental blood heretofore discarded can be collected and sent to depots for the preparation of plasma and the storage of this valuable therapeutic agent.

Dr. John G. Murray, Jr., was responsible for the initiation of this investigation.

#### REFERENCES

- (1) Polayes, S. H., Lederer, M., and Wiener, A. S.: *J. Immunol.* 17: 545, 1929. (2) Wiener, Alexander S.: *Blood Groups and Blood Transfusion*, ed. 2, Springfield, Ill., Baltimore, Md., 1939, C. C. Thomas. (3) Scudder, John: *Ann. Surg.* 112: 502, 1940. (4) Dunn, Cecil G.: *Am. J. Hyg.* 26: 46, 1937. (5) Elliott, John, Busby, G. F., and Tatum, W. L.: *J. A. M. A.* 115: 1006, 1940. (6) Fine, Charles S., Alter, Robert L., and Baptisti, Arthur: *Am. J. Obst. & Gynec.* 39: 462, 1940. (7) Boland, C. R., Craig, N. S., and Jacobs, A. L.: *Lancet* 1: 388, 1939. (8) Goodall, J. R., Anderson, F. O., Altimas, G. T., and MacPhail, F. L.: *Surg., Gynec. & Obst.* 66: 176, 1938. (9) Gey, George O., and Gey, Margaret K.: *Am. J. Cancer* 27: 45, 1936. (10) Carrel, A., and Ebeling, A. H.: *J. Exper. Med.* 38: 419, 1923.

### MANUAL REMOVAL OF THE PLACENTA

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THE frequency with which manual removal of the placenta is performed differs considerably in the reports of various clinics. The range of variation is given as between 0.051 per cent and 3.25 per cent (Table I).

A study of the available statistics seems to indicate that no marked change in the frequency of manual removal has occurred in recent years. Between 1883 and 1918 figures range from 0.34 per cent to 1.8 per cent; from 1928 on, between 0.3 per cent and 3.27 per cent.

Notwithstanding the apparent absence of change in incidence, the number of maternal deaths due to manual removal has sharply decreased in recent years. A review of the literature (Table I) indicates a mortality range in the older reports of between 10 per cent and 15.4 per cent. In contrast to this, the more recent reports indicate that the mortality rate varies from 1.5 per cent to 5.0 per cent, with an absence of fatal results in some of the more recent series.

92 beats per minute. Fig. 3 shows the steady rise in blood pressure which followed. The blood pressure just after the plasma had been given was 110 systolic and 80 diastolic with a pulse rate of 100 beats per minute. Six hours later the blood pressure was 100 systolic and 60 diastolic. Convalescence was uneventful and a transfusion of whole blood was not necessary.

In all of the patients, satisfactory results were obtained with adequate dosage and in not a case was there any systemic or local reaction following the administration of the placental plasma. This was true despite the fact that the placental plasma used in some of the cases was less than twenty-four hours old. In some it had been diluted with 5 per cent glucose in normal salt solution and stored from two to thirty days, while in others it has been frozen and subsequently liquefied for intravenous administration. In others it had been desiccated and given in a concentration four times normal.

Encouraged by our results, we have built an inexpensive but extremely satisfactory dehydration apparatus, to be described in a later publication. The dried placental plasma used in the above cases was prepared by this method. At present we are dehydrating pooled placental plasma obtained from the obstetric service of another hospital as well as from our own, and have demonstrated to ourselves that this is very practical; and for this reason we feel that in a time of a National emergency placental blood from several hospitals in a large city could be transported to central depots for the preparation and storage of plasma in quantities. We are now dehydrating placental plasma for storage and for further clinical investigation, particularly with reference to the effect of dried placental plasma on wound healing, following the suggestion made personally to us by Gey and Gey who have reported<sup>9</sup> the use of placental serum over a period of twelve years for the growth of cells in continuous culture and have demonstrated a "growth sustaining" substance in placental serum. This is in contradistinction to the "growth inhibiting" substance found to be present in adult serum by Carrel and Ebeling.<sup>10</sup> If our preliminary experiments are substantiated, the use of dried placental plasma locally to stimulate cell growth may offer a definite advance in the treatment of wounds.

#### SUMMARY

A heretofore disregarded source of human plasma\* is discussed together with a method for its collection, preparation, and preservation; the advantages as well as the safety and the therapeutic value of plasma from this source are outlined.

#### CONCLUSIONS

1. Placental blood can be used as a source of human plasma.
2. Placental plasma can be prepared, stored, transported, and used in all ways in which adult plasma can be similarly handled.

\*Since this article was submitted for publication, the author's attention has been attracted to a reference to the use of placental blood as a source of plasma by Mahoney, Kingsley, and Howland: *Ann. Surg.* 113: June, 1941.

born fetus weighing 6 pounds 4 ounces was delivered and the cervical lacerations which extended somewhat were repaired. The placenta failed to separate, and after one hour and twenty-five minutes, because of profuse hemorrhage, manual removal was done with great difficulty and in piecemeal fashion. Following this, the bleeding was controlled but the condition of the patient was only fair.

At 5:45 P.M., about one hour and a quarter later, the patient went into profound shock and suddenly died. Permission for autopsy could not be obtained and no pelvic examination was made, so the possibility of uterine rupture cannot be ruled out.

*Comment.*—Several errors in the handling of this case are obvious. The attempt to deliver the patient with a partially dilated cervix, and the delay in the manual removal in the face of active bleeding both contributed to bring about this fatality.

An excellent example of improper treatment with a failure to utilize blood transfusions and early removal of an adherent placenta is demonstrated by the following case history.

CASE 2.—R. B., aged 26 years, primigravida; estimated date of confinement was Sept. 10, 1938. The prenatal course was entirely uneventful until September 15, when at 6:00 A.M. she was found unconscious on the floor at home, in a pool of blood (estimated blood loss at this time was 500 c.c.). On admission to the private maternity division, she was bleeding moderately, the pulse was rapid and feeble, but the blood pressure was 120/80. The fetal heart could not be heard. Examination revealed a fully dilated cervix, with the membranes bulging, and the head high. The membranes were ruptured, the head descended into the pelvis, and bleeding ceased. Blood loss in this period, since admission to the Hospital was between 800 and 1,000 c.c. At 8:25 A.M. spontaneous delivery of a stillborn fetus weighing 6 pounds 10 ounces occurred, and immediately following delivery of the child hemorrhage again became profuse. The placenta could not be expressed by rather vigorous Credé method.

At this time the pulse was imperceptible, the patient cyanotic, and in a marked state of shock. Intravenous glucose, caffeine, Trendelenburg position, and external heat were all utilized. Bleeding persisted and respirations ceased at 9:40 A.M. The placenta removed after death was very adherent, partially separated, and came away from the uterine wall piecemeal.

#### MORBIDITY

Infection complicated the puerperium in 26 (41.93 per cent) of the 62 cases of retained and adherent placentas. Puerperal morbidity is high in most of the series reported, varying from 15 to 80 per cent. It is noteworthy that in the six instances in which spontaneous separation of the placenta finally occurred, only once did elevation of temperature occur in the puerperium; that patient developed a severe thrombophlebitis in the left leg and remained in the hospital for sixty days.

Letinsky (1935) and Block (1937) found that the frequency of morbidity was greater among cases of retained or adherent placentas necessitating manual removal after an operative delivery than in those

TABLE II. MORBIDITY

NORMAL DELIVERIES	LETINSKY	BLOCK	MOLDAVSKY AND SOLOWAY
Noninfected	12%	23.2%	32.30%
Operative deliveries	18%	54.4%	46.15%

This decrease in maternal mortality is understandable when considered in the light of more recent additions to the obstetrician's armamentarium, notably, intravenous glucose, blood transfusions, more widespread use of intravenous oxytocics, and the tendency to perform manual removal before and not after the symptoms of shock have supervened. The appropriate treatment of shock due to loss of blood is today more and more recognized as being most necessary before manual removal is attempted.

TABLE I. LITERATURE ON MANUAL REMOVAL OF THE PLACENTA

AUTHOR	YEAR	TOTAL NO. OF DELIVERIES	NO. OF MANUAL REMOVALS	INCIDENCE %	MORTALITY %	MORBIDITY %
Ssolowjew	1883-1918	304,192	2,912	0.95		
	1918-1933	179,717	2,527	1.40		
Adlerakraus	1894-1907	40,000	452	1.13	0	
Leo	1910	22,250	329	1.48	7.9	
Alletsee	1912	7,125	131	1.80	7.7	
Brandt	1917		30	1.8	0	34.4
Baum	1900-1920	20,418	248	1.20	2.8	34.7
Borberg	1910-1918		50		10.0	60.0
Goethals	1924	16,486	60	0.36	6.6	
Laubenberg	1929	30,000	780	2.60	1.85	
Johannsen	1931	500	26	5.2	0	
Currie	1932				15.4	
Fahlbusch	1932	81,175	1,050		3.15	
Sejrsai	1934			0.51	1.7	80.6
Granzow	1934			1.94	1.6	
Karlin	1935			1.15	0.0	12.1
Peckham	1935				10.7	
Kristensen	1935	16,137	208	1.30	2.0	49.2
Letinsky	1935			2.20	2.0	20.0
Block	1937	50,545	386	0.76	3.6	
Schie		17,133	189	1.10	1.58	
Littaver		10,978	59	0.54	3.4	
<i>Older Mortality Statistics Cited by Eastman</i>						
AUTHOR				MORTALITY %		
Rosenthal, 1899-1900				13		
Vogel, 1903				13.5		
Hegar, 1862				11.0		

We were able to accumulate from a total of 7,132 deliveries 62 cases of retained and adherent placentas in which 56 manual removals were performed, an incidence of 0.78 per cent. Twenty-four of these were service cases, the rest were patients on the private pavilion. Out of 56 cases of manual removal performed, there was one maternal death, a mortality rate of 1.78 per cent.

CASE 1.—B. S., aged 33 years, a tertigravida. The first pregnancy terminated in the delivery of a stillborn fetus, and the second (two years later) in a live child delivered by cesarean section, performed because of a transverse presentation. On Sept. 11, 1939, at 5:25 A.M. she was admitted to the private maternity in active labor with ruptured membranes, and a diagnosis of a footling presentation was made. At 3:05 P.M. delivery from below was attempted although dilatation of the cervix was not complete. The feet and trunk were extracted, but the delivery of the head was impossible until Dührssen's incisions were made. A still-



TABLE IV. COMPLICATIONS OF PRENATAL PERIOD

COMPLICATION	NO. OF CASES	PER CENT
Toxemia	9	47.36
Breech presentation	4	21.05
Late ante-partum hemorrhage	3	15.78
Threatened abortion	2	10.52
Pyelitis	1	5.26

The unusual incidence of late post-partum hemorrhage is worthy of note. The significance of the increased frequency of breech presentations is not clear.

*Labor.*—The average duration of labor was twenty-three hours and twenty-three minutes, and varied from two hours to three days. As was expected, labor was characterized by a definite tendency to uterine inertia. In nine instances this was the only apparent basis for prolonged labor. As a matter of fact in this group, the average length of labor was fifty hours. The average duration of the third stage of labor was one and one-half hours, and ranged in length from fifteen minutes to four hours and fifteen minutes.

In 46 instances, the placenta was described as being adherent, fibrotic, and difficult to separate from the uterine wall. The placenta was retained in 10 cases, and in all of these was described as being free in the lower uterine segment. In 6 of the records there was no description of the presence or absence of true adherence of the placenta to the uterine wall.

TABLE V. INDICATIONS FOR MANUAL REMOVAL

INDICATIONS	NO. OF CASES	PER CENT
Hemorrhage	20	32.25
Unsuccessful Credé	22	35.49
Other causes:		
Toxemia, prompt delivery	9	14.15
Hourglass cont. of uterus		
Delayed separation		
(More than 1 hr.)		

Severe hemorrhage complicated the deliveries in 20 cases, or 42 per cent, blood loss varying from 500 to 1,800 c.c. Only one of these was in the retained placenta group, the rest all occurred in those instances in which the placenta was adherent and fibrotic in character. Transfusions were given in 11 of these cases, almost 50 per cent.

*Remote Sequelae.*—Schie, by means of mailed questionnaires to all the patients in his series on whom manual removal of the placenta had been performed, found that out of 145 patients, 32, or 21.9 per cent, were living in involuntary sterile marriage.

Through the cooperation of our Social Service Department we were able to obtain accurate follow-up studies on 13 of the 24 ward cases.

Seven had become pregnant since the manual removal performed in every instance following a first pregnancy. In greater detail their stories are as follows:

CASE 1.—H. P., 25 years of age. First pregnancy in 1938 with manual removal of the placenta; second pregnancy in 1940. The second pregnancy was complicated

in whom the placenta was delivered manually following spontaneous delivery. A similar conclusion can be drawn from our own series.

*Fetal Mortality.*—Four fetal deaths (6.45 per cent) occurred. Two were deaths in utero, one because of nephritic toxemia and the other due to premature partial separation of the placenta. The other two were premature babies which died during the neonatal period.

*Parity.*—The fact that the patients in this series were almost exactly evenly divided into primiparas and multiparas seems to rule out parity from the list of possible etiologic factors responsible for adherent and retained placenta. Of significance, however, is the fact that of the women who were pregnant for the first time, 17 or more than half, were elderly primiparas. This adds but another unfavorable possibility to the hazards of pregnancy in this age group.

*Obstetric History.*—An abnormal obstetric background was found in 22 cases (35.48 per cent). Table III shows that in thirteen instances, or 59.09 per cent of the cases with previous pathology, there was a history of one or more septic abortions.

TABLE III. OBSTETRIC BACKGROUND

NAME	AGE	GRAVIDITY	OBSTETRIC BACKGROUND
L. B.	33	iii	One miscarriage
T. W.	27	ii	Breech
J. B.	23	iv	One ectopic pregnancy, two miscarriages
K. B.	23	ii	Six abortions (one infected)
S. T.	23	iv	Three infected abortions
M. S.	30	iv	One miscarriage
R. E.	28	ii	One premature labor
M. P.	34	ii	Pyelitis of pregnancy
L. K.	27	ii	One miscarriage
J. R.	21	ii	Neonatal death
M. G.	30	iv	One miscarriage
A. K.	25	ii	Breech, premature labor
J. D.	21	iv	Dilatation and curettage after third pregnancy
A. A.	31	ii	Section for fractured pelvis
B. S.	31	ii	Two miscarriages
S. T.	29	ii	Induced abortion
D. S.	30	ii	Manual removal with first pregnancy
D. B.	31	ii	Incomplete abortion
F. E.	30	iii	High forceps with first pregnancy
E. K.	21	ii	Dilatation and curettage after miscarriage
M. S.	24	ii	Premature labor
R. R.	28	ii	One miscarriage

The frequency of previous uterine infection, with probable injury to the uterine endometrium lends credence to the concept of intrauterine abnormality as a predisposing agent in the production of an adherent placenta.

*Prenatal Period.*—The prenatal course of 30 per cent of the patients comprising this series exhibited abnormal trends. From Table IV it is evident that toxemia of pregnancy was by far the most frequent complication.

4. Fetal mortality occurred four times (6.6 per cent), twice in utero, and twice neonatally in premature infants.

5. Morbidity complicated the puerperium in 42 per cent of the cases, and was higher in the group of patients delivered by operative means.

6. The large number of elderly primiparas in this series adds another possible complication to the hazards of pregnancy in this age group.

7. The frequency of previous septic abortions and miscarriages adds strength to the concept of abnormal uterine status as a cause of adherent placenta.

8. Toxemia, pyelitis, and late post-partum hemorrhage were the most common prenatal complications.

9. Uterine inertia was an important complicating factor in labor which was prolonged in this series.

10. The most important immediate sequelae seem to be hemorrhage and sepsis.

11. The most common secondary sequelae seem to be sterility, abortion, and ante-partum hemorrhage in subsequent pregnancies.

We wish to thank Dr. M. W. Aaronson, Chief of Service, for his kind assistance. We are deeply grateful to Dr. M. A. Novey, Assistant Professor of Obstetrics, University of Maryland, for his invaluable aid in the composition of the manuscript.

#### REFERENCES

*Block, E.*: Acta obst. et. gynec. Scandinav. 17: 343, 1937. (See for Review of Literature.) *Kristensen, B.*: Acta obst. et gynec. Scandinav. 15: 1935. *Leo, A.*: Beitr. z. Geburtsh. u. Gynäk. 15: 1910. *Zangemeister*: München. med. Wchnschr. 13: 338, 1921. *Eastman, N. G.*: Internat. Clin. 3 (Series B): 264, 1939. *Schie, E.*: Acta obst. et gynec. Scandinav. 19: 28, 1931.

## THE ROLE OF CESAREAN SECTION IN THE TOXEMIAS OF PREGNANCY\*

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WITH the development of low cervical cesarean section in the past twenty years, there has been an increasing tendency toward combined medical and surgical treatment for toxemia of pregnancy. By this condition, we refer to that state characterized by the presence of at least two of the following symptoms: hyperpiesia, with a blood pressure of 140 systolic and 90 diastolic or higher; peripheral edema, and albuminuria, accompanied or not by a cardiovascular or renal component. In an attempt to evaluate the efficacy of this treatment, we made a study of the cesarean sections done for toxemia of pregnancy in the Michael Reese Hospital during the ten-year period of 1929 to 1939. We should like to preface our report by stating that in all cases the operation performed was a laparotrachelotomy, a procedure which has been in popu-

\*Read at a meeting of the Chicago Gynecological Society, March 21, 1941.

by premature separation of the placenta three weeks prior to term, with an estimated blood loss of 1,000 c.c. Spontaneous birth of a live baby occurred.

CASE 2.—M. R., 35 years of age. First pregnancy in 1928 with manual removal; four pregnancies since (1929, 1930, 1931, 1935). No difficulties, all spontaneous deliveries, the placenta separated spontaneously and quickly after each delivery.

CASE 3.—M. T., 23 years of age. First pregnancy in 1938; second pregnancy in 1940. Forceps delivery, spontaneous separation of placenta within ten minutes after delivery of the baby.

CASE 4.—B. P., 23 years of age. First pregnancy in 1937. At present six months pregnant, uneventful to date.

CASE 5.—G. F. First pregnancy in 1935; second pregnancy in 1936. Second pregnancy terminated in spontaneous abortion. Has desired to become pregnant since, and cannot.

CASE 6.—D. S., aged 31 years. First pregnancy in 1938. Delayed separation of the placenta, with her second pregnancy in 1940. Spontaneous separation occurred after a thirty-seven-minute waiting period.

CASE 7.—D. H., aged 24 years. First pregnancy in 1940. The patient was re-admitted to the dispensary April 28, 1941, about five months pregnant. Because of the complications that marred her first pregnancy, namely, toxemia, manual removal, and thrombophlebitis, she was followed at two-week intervals. On May 13, 1941, the sixth month of her pregnancy, she was admitted to the ward, with a history of vaginal bleeding and with irregular pains. She went into active labor and after thirteen hours and thirty minutes, delivered spontaneously a premature still-born child, breech presentation. The fetus showed softening of the skull bones and maceration of the skin. Immediately after birth of the child there was a fairly profuse hemorrhage (500 c.c.). Repeated attempts to express the placenta were unsuccessful, and after one hour hemorrhage again became severe. Manual removal was decided upon and carried out. The procedure was made difficult by the presence of a moderate Bandl's ring which, however, relaxed under anesthesia. The placenta was firmly adherent to the uterus, and was removed only with great difficulty. Bleeding ceased and the uterus was firmly packed. The patient's condition was good, her blood pressure was 118/40. Pathologic examination of the placenta revealed no abnormalities in structure except for numerous infarcts. The intrauterine pack was removed in twelve hours, and there was no further bleeding. On the second day, 500 c.c. of blood were given to facilitate recovery. The patient was discharged after an afebrile hospital stay of ten days.

Six of the women investigated have not as yet become pregnant. Of these, 2 (33 per cent) desire pregnancy, but have remained sterile. Four are practicing voluntary contraception.

In total then, 6 of the 13 patients, or 46.15 per cent, show apparent after-effects of the manual removals performed on them, in terms of hemorrhage, abortion, or sterility.

#### CONCLUSIONS

1. Sixty-two cases of retained and adherent placenta with 54 manual removals have been presented.

2. The incidence of manual removal was 0.78 per cent, agreeing with the general average in the literature.

3. There was one maternal death, an uncorrected mortality of 1.78 per cent.

cylindruria 2-plus, and a nonprotein nitrogen content of the blood of 48 mg. per hundred cubic centimeters. The ocular findings were negative. The patient was placed under conservative management, including venesection with removal of 500 c.c. of blood. Four days after admission she continued to complain of severe headache and spots before the eyes. A bag induction was attempted but was not successful, after which a low cervical cesarean section was performed under ethylene anesthesia. On the fourth postoperative day, the patient showed signs of uremia and twitching, and the nonprotein nitrogen content of the blood was 62 mg. and the creatinine 2.9 mg., per hundred cubic centimeters of blood. The blood pressure at this time was 214 systolic and 140 diastolic. Forty-eight hours later the patient went into coma and died. This death accounted for our maternal mortality of 1.06 per cent.

TABLE II. CESAREAN SECTION FOR TOXEMIA

AUTHOR	MATERNAL MORTALITY PER CENT	FETAL MORTALITY PER CENT
Peterson, R.: J. Michigan M. Soc. 13: 4, 1914	35	None given
Holland, E.: J. Obst. & Gynaec. Brit. Emp. 38: 358, 1921.	31.8	46.9
Gordon, C. A.: AM. J. OBST. & GYNEC. 16: 307, 1928.	12.9	21.9
Tucker, S. B.: Texas State J. Med. 30: 591, 1935	6.25	6.25
Irving, F. S.: Canad. M. A. J. 40: 137, 1939	2.5	None given
Present series	1.06	13.5

A review of the literature (Table II), shows that with succeeding years the maternal mortality from cesarean section in cases of toxemia has been greatly reduced. We must bear in mind, of course, that this reduction has been due primarily to improved asepsis, increased surgical proficiency, and better obstetric judgment, as well as to a decided trend to low cervical cesarean section.

There was one nonoperative death due to toxemia of pregnancy. Including the death following cesarean section, the total maternal mortality was 0.43 per cent as compared with a 1.7 per cent maternal mortality in hospitals throughout the United States.

In the report of the United States Bureau of Census, it is stated that late toxemias of pregnancy cause annually 20 per cent of approximately 10,000 maternal deaths throughout the country. At the Michael Reese Hospital there were 35 maternal deaths in this ten-year period, 2, or 5.7 per cent, of which were of toxemic patients.

#### FETAL MORTALITY

It is generally agreed that the mortality of premature babies born of toxemic mothers is lower when these infants are delivered by cesarean section than by the vaginal route. It is especially true that toxemic babies do not tolerate labor well. There were 55 premature infants in the series, weighing between 900 and 2,500 Gm.; the remaining 41 infants weighed 2,500 Gm. or over. The gross fetal mortality was 13.5 per cent. The fetal mortality in infants weighing between 900 and 2,500

TABLE III. INCIDENCE OF VARIOUS TYPES OF TOXEMIAS

	NO. OF CASES	PER CENT OF CESAREAN SECTIONS
Pre-eclampsia	70	72.0
Eclampsia	6	6.3
Nephritic toxemia	8	8.5
Cardiovascular disease	3	3.2
Other toxemias	7	7.4
Total	94	

lar use in this clinic for the past fifteen years because of its ease of performance, practicability, and safety.

No doubt the old classic section, under general anesthesia, had a higher mortality than medical treatment with pelvic delivery. It is possible that the laparotrachelotomy, under local anesthesia, has reduced the operative mortality to the extent that this operation may now be used more often. The results in the group of cases to be reported may tend to prove this likelihood. All the operations were done by eleven operators on both the private and the ward services. During this ten-year period, 681 cesarean sections were performed in a total of 15,555 deliveries, the indication being toxemia in 94. From 1922 to 1927 4 cesarean sections were done for toxemia, as compared with 57 in the following five years, 1927 to 1932.<sup>1</sup> The number of cesarean sections for toxemias from 1929 to 1939 varied from 6 to 15 a year, as shown in Table I.

TABLE I

YEAR	TOTAL NO. OF C. S.*	NO. OF PATIENTS WITH TOXEMIA	C. S. FOR TOXEMIA	% OF PA- TIENTS WITH TOXEMIA TREATED BY C. S.	% OF C. S. DONE FOR TOXEMIA
1929	72	59	15	25	21
1930	77	48	9	19	12
1931	67	40	6	15	10
1932	47	39	7	19	15
1933	39	37	6	16	20
1934	68	35	7	20	10
1935	59	40	8	20	14
1936	87	62	9	15	10
1937	89	51	13	26	15
1938	76	53	14	26	18
Total	681	464	94	20	14

\*C. S., cesarean section.

#### INCIDENCE

Of 681 cesarean operations in this series, 94, or 14 per cent, were done for toxemia of pregnancy; 6 for eclampsia and the remaining 88 for pre-eclampsia and other allied toxemias. Hospital figures give the incidence of nonconvulsive toxemia of pregnancy in the United States as varying between 0.2 and 29 per cent, or an average of 4 per cent.<sup>2</sup> The incidence given by Allen in his discussion of the study of Dieckmann and Brown<sup>2</sup> was 6.2 per cent; and we found toxemia in 3 per cent of all admissions in the period under investigation, i.e., 464 cases of late toxemias in a total of 15,555 deliveries. In 94, or 20 per cent, of these cases, the pregnancy was terminated by cesarean section. Dieckmann and Brown<sup>2</sup> cited an incidence of cesarean operations of 16 per cent in the Chicago Lying-in series. Of the 94 patients in our series, 68, or 72 per cent, were primiparas, and 26, or 28 per cent, were multiparas. Delivery was premature at thirty-seven weeks or less in 52 cases, or 55 per cent of all the cases in which operation was performed.

#### MATERNAL MORTALITY

There was one maternal death in the group under study. The patient was a 40-year-old gravida iv, para iii, in her twenty-eighth week of pregnancy, who had severe pre-eclampsia, superimposed on chronic glomerulonephritis. She had made one prenatal visit before admission to the hospital. Her blood pressure on admission was 256 systolic and 160 diastolic, and she complained of irregular headaches and spots before the eyes. Significant laboratory findings were albuminuria 3-plus,

2. In the period under investigation, 5.7 per cent of all the maternal deaths were due to toxemia.

3. The maternal mortality in this study was 1.06 per cent.

4. The maternal mortality from all the toxemias of late pregnancy, including eclampsia, in the same period was 0.43 per cent.

5. The fetal mortality in the entire series was 13.5 per cent. The premature infant mortality was 20 per cent, and the mature infant mortality, 4.8 per cent. The mortality rate of premature infants delivered vaginally has been given as 47 per cent.

6. The incidence of cesarean section done for toxemia increased from 4, in five years from 1922 to 1927, to 94 in the ten-year period from 1929 to 1939.

7. Twenty per cent of the toxemie patients were delivered by cesarean section in this same ten-year period.

### CONCLUSION

It is our impression that when the toxemia progresses, in spite of medical treatment, and the fetus is viable, it is more radical to carry the patient nearer to term in selected cases than to perform low cervical cesarean section. It would appear that the latter procedure carries a lower maternal and fetal mortality and alleviates undue strain on the cardiovascular-renal apparatus. Future studies may bear out this contention.

### REFERENCES

- (1) *Stein, I. F., and Levinthal, M. L.*: AM. J. OBST. & GYNEC. 30: 192, 1935.
- (2) *Dieckmann, W. J., and Brown, I.*: Ibid. 38: 214, 1939. (3) Report of the American Committee on Maternal Welfare, J. A. M. A. 104: 1703, 1935.

### DISCUSSION

DR. WILLIAM J. DIECKMANN.—Excluding those cases where there is definite cephalopelvic disproportion, I believe cesarean section is occasionally indicated in the treatment of severe toxemia of pregnancy where either the patient has not been seen by a doctor or the doctor has adhered too long to medical management. Reports on the use of cesarean section in the treatment of eclampsia reveal that the maternal mortality ranges from two to 88 per cent.

According to Holmes, the mortality from cesarean section in the United States is 5 per cent. The average mortality for eclampsia is 13 per cent. Thus if the two conditions are present in the same patient, the mortality may be quite high. One reason for this high mortality is that the contraindications to cesarean section are not always recognized. In a period of nine years, 1,349 cesarean sections were performed in the Chicago Lying-in Hospital with an uncorrected maternal mortality of 0.67 per cent and a corrected one of 0.45 per cent. This low mortality rate has been achieved by recognizing that there are definite contraindications to laparotomies. This operation is not performed if the membranes have been ruptured over twenty-four hours; if the patient has been in labor over twenty-four hours; if attempts have been made to induce labor by some mechanical means; if forceps or version have been attempted; or if the patient's temperature is elevated.

Cesarean section is used in toxemic patients; (1) if there is cephalopelvic disproportion, (2) after medical treatment has been used in severe pre-eclamptic or eclamptic patients who are near term with a closed, uneffaced cervix, and (3) in patients with severe vascular or renal disease if termination is deemed necessary between thirty-two and thirty-eight weeks' gestation. Sterilization per se is not an indication. Cesarean section should not be used as a last resort.

Gm. was 20 per cent; in those infants weighing above 2,500 Gm., it was significantly lower, 4.8 per cent. The fetal mortality in premature infants delivered vaginally has been given as about 47 per cent.<sup>2</sup> Table II shows the fetal mortality of cesarean section for toxemia.

#### INDICATIONS

Toxemia of pregnancy was the primary indication in all of these cesarean sections. Table III classifies the number and percentage of the various types of toxemias.

These cases represent both the private and the ward services of eleven operators. Most of the patients were hospitalized and given a thorough trial of conservative treatment. This treatment was quite uniform, consisting of sedation by the Stroganoff technique, absolute bed rest, restricted diet, purgation, and intravenous administration of dextrose; more recently magnesium sulfate has been used hypodermically or intravenously. The large percentage of patients subsequently operated upon represents cases in which, despite adequate medical management, the toxemia was progressive or stationary and the pregnancy thirty-two weeks or beyond, with the fetus viable. Low cervical cesarean section was performed in all these cases. Seventy-two per cent of the cesarean sections for toxemia were done on primiparas. The majority of multiparas have some dilatation, and if feasible, labor is induced and the patient delivered vaginally. Cesarean section is done on primiparas and multiparas in those cases in which the toxemia does not improve, the fetus is viable, and the cervix unripe for vaginal delivery. Local anesthesia was used in 40 per cent of the cases. The other anesthetics employed were induced by the following agents, named in the order of their frequency: ethylene, ethylene and ether, local anesthesia and ethylene, cyclopropane, and spinal anesthesia.

#### COMMENT

A combination of medical and surgical treatment was used in the cases of cesarean section for toxemia in this study. Dieckmann stated that cesarean section should be used only in the pre-eclamptic patient when eclampsia seems imminent and when delivery through the vagina seems unwise. We are of the opinion that it is an unnecessary risk to both the mother and the baby if the toxemia is allowed to reach a point where eclampsia is imminent, and that cesarean section should be performed at the earliest time consistent with the safety of the baby if the toxemia is progressive or does not improve in spite of hospital medical treatment. With the advent of low cervical cesarean section under local anesthesia and its low mortality, we think this procedure safer for the mother and the infant than awaiting the approach of eclampsia.

We also believe, as does Horner<sup>2</sup> that the sooner an unborn baby within the period of viability is separated from its toxemic mother, the better is its chance for life; and, conversely, the longer it is attached to its toxemic mother, the less likely it is to survive.

We agree with the statement from the American Committee on Maternal Welfare<sup>3</sup> that the long-continued toxemia of pregnancy is more productive of chronic arterial and renal disease than toxemia of short duration. We believe that if more of the patients in our study had been delivered vaginally, the maternal and fetal mortality would have been higher.

#### SUMMARY

1. A series of 94 cesarean sections done for toxemia of pregnancy at Michael Reese Hospital in the ten-year period from 1929 to 1939 is reported.



In our clinic we believe that if this convulsive type appears as a fulminating, rapidly advancing toxemia that immediate cesarean section is the safest way out for mother and baby. Those patients who have the slightest evidence of advancing toxemia that is not controlled by dietary advice on home management are immediately hospitalized and put under strict medical management, and then if they do not improve we deliver by medical or mechanical induction of labor or cesarean section as best suits the case.

We use local anesthesia on all the nonconvulsive types, but not on the convulsive type, because we feel that a general anesthesia prevents convulsions while we are operating, which avoids many undesirable complications.

We do not believe that there is a great deal of evidence of improvement in statistics due to low cervical section as far as our experience goes. The group in which we have done low cervical section has about the same mortality as the group in which we have done the classical section. We have now something over 70 eclamptic toxemic patients who have been delivered by cesarean section, every other one a low cervical and every other one a classical. These cases were done in the same operating room with the same nursing personnel, the same doctor, and the same technique, and we got about the same results.

The rule in my clinic is that we never do cesarean section on eclamptic patients if we can avoid it. We do it in all cases in which we feel the danger of allowing the patient to go further in pregnancy is greater than the danger of doing the operation. The greatest danger is in procrastination, in trying to get the obstetrician to make up his mind, that there is an indication present that will be defensible if he does a cesarean section and loses the case. We have had fewer deaths in the patients operated upon, convulsive and nonconvulsive, than in those treated conservatively.

## AN ELEVEN-YEAR SURVEY OF CESAREAN SECTION AT A SMALL COMMUNITY HOSPITAL

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THIS study of cesarean sections performed at the Mount Vernon Hospital is presented not with the intention of illustrating inferiority or excellence of results obtained, but rather to further the thought that in order to evaluate properly the status of abdominal section, considerably more attention must be paid to the preparing and publishing of such surveys from smaller hospitals.

The surveys and statistical results obtained from the leading obstetric clinics are well publicized, appreciated, and duly admired. They represent the par for the course. Excellently staffed, well-equipped, and with all decisions and techniques under the direct control of obstetric specialists, it is only reasonable to expect superlative results. However, the bulk of obstetric practice does not take place in these leading centers. It is largely entrusted to the hands of the small, moderate-sized voluntary and community general hospital, wherein every general practitioner does his "confinement work" and thereby directly influences the incidence, type morbidity, and mortality of abdominal delivery.

This survey represents the eleven-year study of cesarean section in such a 200-bed community hospital in which fifty-odd general practitioners "do obstetrics" and when in trouble call upon the services of several surgeons or obstetricians to help them out. This situation un-

The average mortality for eclampsia is 13 per cent and for nonconvulsive toxemia is 1.7 per cent. The patient who has not had convulsions is obviously a better risk than if convulsions once develop. Therefore, as Dr. Strauss has emphasized, it is much better to perform a cesarean section on the pre-eclamptic than on the eclamptic.

Seventeen per cent of 1,672 toxemia patients had the pregnancy terminated by laparotomy. Hysterotomies are included. In the period from 1931 to 1936, this figure was 21 per cent. In the next two years it was 14 per cent and in the period from 1938 to 1939 it was 9 per cent. Our incidence of hysterotomy and cesarean section in the treatment of pre-eclampsia is 11 per cent, in hypertensive disease 21 per cent, in nephrosclerosis 56 per cent and in glomerulonephritis 45 per cent. Eighteen per cent of 75 eclamptic patients had a cesarean section in our hospital. The decrease in the use of cesarean section is due to more intensive treatment of the ambulatory patient and earlier hospitalization if the toxemia does not respond to home management.

Over 20 per cent of our cesarean sections were performed for some other indication than toxemia. Forty-four per cent of the operations were in primiparas, a much lower figure than that reported by Dr. Strauss.

Eclampsia was present in 10 per cent, pre-eclampsia in 48 per cent, and vascular-renal disease in 13 per cent. In the multipara, pre-eclampsia was present in 10 per cent and vascular-renal disease in 49 per cent.

Dr. Strauss has stated that delivery through the vagina may increase the fetal mortality in toxemic patients. In general, our data, as well as those of Clifford from the Boston Lying-in, do not support this belief. The following data indicate that cesarean section is associated with a fetal mortality which is definitely higher than that associated with vaginal delivery. Of course, the number of severe toxemias is greater in the cesarean group, which would account for part of the increase in fetal mortality. There has been a steady decrease in our fetal mortality which we ascribe to the use of local anesthesia, the omission of all drugs which might interfere with fetal respiration, and the immediate transfer of the baby, if premature, to the Hess incubator.

The total fetal mortality for laparotomy was 17 per cent; for babies weighing over 1,000 Gm., 12 per cent; over 1,500 Gm., 11 per cent; and over 2,500 Gm., 6 per cent. The fetal mortality for babies weighing over 1,500 Gm. for the period from 1931 to 1936 was 12 per cent and for the next three years was 4, 4, and 3 per cent, respectively. Fetal mortality is also dependent on the type of maternal disease. Thus, in mild toxemia, fetal mortality is 7 per cent, in severe pre-eclampsia 17 per cent, in severe hypertensive disease 27 per cent, in nephrosclerosis 39 per cent and in glomerulonephritis 58 per cent.

Dr. Strauss has stated that long-continued toxemia is likely to be followed by chronic vascular-renal disease. I take exception to this statement. It is my experience that a patient with severe pre-eclampsia cannot be carried for weeks. If such a patient can be carried for a period of several weeks, the condition is one of hypertensive disease and obviously such a patient may have a persistent hypertension after delivery or a recurrence of the toxemia in a subsequent pregnancy.

DR. W. H. RUBOVITS.—There is an occasional toxemic patient in whom the conditions are quite ideal for the performance of vaginal cesarean section, especially in a multipara with roomy pelvis and relaxed tissue.

Another point to consider is the advisability of performing a section even though the patient has already developed convulsions. If the convulsion has been mild or easily controlled and a number of hours have elapsed without evidence of the appearance of more convulsions, I think that we should not be deterred by the rule which has been adopted in many clinics that a patient once having developed convulsions should not be sectioned.

DR. FREDERICK H. FALLS.—Dr. Strauss voices pretty much the same opinion that I stressed in 1935 when I reported my first 500 cases of eclamptic toxemia. At that time I admitted that I was heretic in suggesting cesarean section in a large percentage of eclamptic patients, because the overwhelming opinion then as now was against this procedure.

disproportions. In justification, may it be said that proper evaluation of a pelvis is still the most difficult task which confronts the trained obstetrician, not to mention the lack of uterine force and the deficiency of mental and physical stamina with which so many of our modern women approach labor.

It is gratifying to note the marked reduction in sections for eclampsia from 16 per cent in the first group to 4 per cent in the second group.

The hemorrhagic complications of pregnancy were treated by section in both series. This is quite in accord with the best-informed opinion of today.

The smaller number of repeat sections in both groups is striking. Undoubtedly the economic factors attending the depression decade with its marked increase in elderly primiparas has precluded further pregnancy in this group.

The group of sections done primarily in the interest of the child shows a marked increase in the second series. As the typical American family shrinks in size, the value of each baby proportionately increases. The elderly primigravida with breech presentation or the sterility problem which has finally become pregnant after much expense is not in a mood to gamble with the safety of the child when confronted with the possibility of its loss.

TABLE III. COMPARATIVE INDICATION STATISTICS

INDICATIONS	MOUNT VERNON, N. Y. 8,459 DELIVERIES 204 SECTIONS, 2.6%	CHICAGO LYING-IN 18,000 DELIVERIES 1,000 SECTIONS, 5.5%
Disproportions and dystocia	44.0%	47.0%
Placenta previa	10.6%	7.9%
Abruptio placentae	4.3%	4.6%
Eclampsia	9.6%	0.9%
Pre-eclampsia	1.9%	6.5%
Repeat section	8.0%	28.0%

Table III gives a comparative analysis of the indications at our hospital and those of a large obstetric center. The marked disparity in the figures for eclampsia is obvious. The tendency in the first series was to operate during the stage of convulsions. In the second series, we too learned but apparently not enough to treat the eclampsia medically when fully developed. We are also learning that section may be the very best way of treating pre-eclampsia, particularly in the untried pelvis. The striking difference in repeat sections is noteworthy. This, of course, contributes to the larger cesarean percentage figures for the obstetric center and by dilution with clean, uninfected cases improves the morbidity statistics for the larger center.

TABLE IV. TECHNIQUE USED

TYPE OF OPERATION	GROUP I 1930-1935 97 SECTIONS	GROUP II 1936-1940 107 SECTIONS
High classic	31%	15.0%
Low classic	36%	25.0%
Double flap	25%	49.0%
Porro	0	4.5%
Latzko	1%	2.0%
Broadhead exclusion	4%	0
Froste-Smith extraperitoneal	0	4.0%

Table IV shows the various types of operations used in the two periods. In Period I, 67 per cent of all sections were of the classic type and but 25 per cent were of the double flap or low segment type. In Period II, only 40 per cent were of the classic type while 50 per cent were of the double flap variety. In addition, 4 per cent of the cases were hysterectomized and 6 per cent were of the extraperitoneal type. In other words, the staff became definitely infection-conscious and progressive attempt was made to preclude peritoneal contamination and infection by getting down into the

doubtedly more truly represents nation-wide conditions. If real improvement in morbidity statistics is to be made, it must, in the final analysis, be obtained by bettering the results of this great group of smaller hospitals. The making and publishing of small hospital surveys will stimulate local interest and community rivalry and will inevitably reflect improvement in end results. To illustrate this point: In 1935, the first five-year survey of sections performed in this hospital was presented to the staff. It showed the appalling mortality rate of 10 per cent. In 1940, the second five-year survey was likewise prepared and reported. It showed the pleasing reduction in mortality to 3.7 per cent. Can anyone gainsay that the critical analysis in 1935 did not at least have a part in achieving this improvement?'

## STATISTICAL ANALYSIS

In period I, the section incidence was 2.1 per cent. In period II, the incidence was 3.1 per cent. For the entire eleven-year period, there were 8,459 deliveries with 204 sections, which is an incidence percentage of 2.6, a fairly conservative figure.

TABLE I. INCIDENCE OF SECTION

PERIOD I. 1930-1935			PERIOD II. 1936-1940		
YEAR	BIRTHS	SECTIONS	YEAR	BIRTHS	SECTIONS
1930	822	19	1936	689	22
1931	823	15	1937	781	17
1932	790	17	1938	752	23
1933	746	14	1939	831	23
1934	635	13	1940	830	22
1935	662	19			
Total	4,478	97		3,883	107

TABLE II. INDICATIONS

	PERIOD I 1930-1935	PERIOD II 1936-1940
Contracted pelvis, before labor, elective	6	15
Dystocia, cephalopelvic disproportion	34	33
Prc-eclampsia	0	4
Eclampsia	16	4
Abruptio placentae, accidental hemorrhage	3	6
Placenta previa	9	13
Repeat section	14	12
Cardiac	4	3
Previous operative repair	3	3
Fibromyoma	4	4
Pulmonary hemorrhage	1	0
Sterilization	1	0
Interest of child	2	9
Chorea of pregnancy	0	1
Total	97	107

Table II presents a comparison of the indications for abdominal delivery in the two series. Several observations are pertinent.

Notwithstanding the availability of x-ray pelvimetry, it is apparently still very difficult for the general practitioner to evaluate properly comparative cephalopelvic proportions. In the two series, there is but little improvement in the number of elective sections for disproportion. Trial of labor was resorted to in the majority of

*Peritonitis*.—All 3 cases ended fatally. All had ruptured membranes and all had been examined vaginally two or more times. One was a classic for partial placenta previa and two were low flaps for dystocia with membranes ruptured for many hours.

Although the low flap operation limits infection in the potentially unclean cases, it apparently is not a preventive for the initial spill in the grossly infected case. Its indication must not be pushed too far. In actually infected cases nothing short of a true extraperitoneal approach should be elected. In this series of 204 sections, 11 true extraperitoneal sections for frankly infected cases suffered no mortality.

Table VI shows the cause of death. In the first period, there were four deaths from shock or hemorrhage. The indications, respectively, were (a) unrecognized rupture of uterus (repeat section-patient allowed to go into labor during night while awaiting elective section following morning), (b) eclampsia operated during convulsion stage without preliminary treatment, (c) central placenta previa uncontrolled by packing, and (d) very prolonged labor. All of these were sectioned by the classic route. Only one had been typed preoperatively and none were transfused in time to prevent death. In the second period, there were no deaths from shock or hemorrhage.

TABLE VI. MATERNAL MORTALITY

CAUSE OF DEATH	PERIOD I	PERIOD II
Shock or hemorrhage	4	0
Peritonitis	5	3
Embolism	0	1
Number of deaths	9	4
Number of cases	97	107
Percentage mortality	10	3.7

In the first period, there were 5 deaths from peritonitis. All had ruptured membranes. All were sectioned by the classic route for dystocia after varying lengths of trial labor. One was further complicated by eclampsia. In this first series, 5 out of 34 patients sectioned for dystocia after rupture of membranes and trial labor died of peritonitis. Strangely enough, in the second period this appalling mortality was not greatly changed. There were 3 deaths out of 33 similar disproportion cases although two were sectioned by the double flap method. It is, therefore, apparent that in this hospital at least any transperitoneal section for dystocia with ruptured membranes and trial of labor carries with it a high mortality rate.

Table VII shows the mortality according to the type of operation used. The figures are too obvious to need much comment. It is, however, true that the less qualified surgeon elects the classic route because of ease of accomplishment and, therefore, puts that operation under the added handicap of his inexperience. On the other hand, it is also true that the suspected infected cases are usually done by the double flap method which should, to a large extent, counterbalance this factor. The case for the true extraperitoneal approach in the slightly infected problem looms larger and larger and will undoubtedly supplant the low cervical section for this type of case.

TABLE VII. MATERNAL MORTALITY

TYPE OF OPERATION	NO. CASES	DEATHS	PER CENT
High classic	46	6	13.0
Low classic	51	4	7.8
Double flap	75	3	4.0
Extraperitoneal	11	0	0
Porro	6	0	0

lower uterine segment, by removing the uterus or by excluding the uterine incision from the peritoneal cavity. The significance of this change in technique will be evident in the mortality tables.

TABLE V. COMPLICATIONS FOR PERIOD II, 107 SECTIONS

COMPLICATIONS	1936-1940 NO. CASES	1936-1940 PER CENT
Phlebitis	7	9.0
Embolism	3	2.9
Atelectasis pneumonia	7	9.0
Wound infection	5	4.8
Shock or hemorrhage	14	12.0
Ileus	5	4.8
Retained placenta	3	2.8
Disruption previous scar	2	1.9
Peritonitis	3	2.8

*Phlebitis.*—This occurred three times as frequently in the cases wherein trial of labor was resorted to.

*Embolism.*—All were pulmonary in type. There were two recoveries and one fatality on the twenty-seventh postoperative day. Two of these cases were clean, elective cases. The fatal case was the only one showing clinical evidence of thrombophlebitis.

*Atelectasis and Pneumonia.*—Fortunately, there were no fatalities in the group. Twelve per cent of nonelective cases showed pulmonary signs, whereas only 4 per cent of the elective were similarly affected.

*Wound Infection.*—All occurred in cases with ruptured membranes and 3 out of the 5 cases were drained at the time of operation on the suspicion of infection already present.

*Shock and Hemorrhage.*—Ten cases showed evidence of moderate shock or hemorrhage postoperatively, whereas 4 cases showed marked shock or hemorrhage. Of these latter, two were complete placenta previas with marked preoperative blood loss, one was a total eclamptic with marked blood loss on the table, and one suffered severe hemorrhage when uterine incision extended through uterine vessels and into vaginal plexus. No fatalities from shock or hemorrhage occurred in this five-year period under consideration. Ninety cases out of 107 were typed before operation and 44 received one or more transfusions. Nearly all received intravenous glucose at the table or on return to their room. This careful attention in preparation for the prevention and early treatment of shock or hemorrhage has greatly improved the results obtained in the first period. At the present time, it is practically routine in this hospital not to begin cesarean operations until a compatible donor is in the hospital.

*Ileus.*—With the exception of the peritonitis cases, ileus was not a prominent finding in this series of cases. It was only severe in two high classic cases and here was quickly controlled by the Wangenstein suction drainage. The diminution in ileus and distention is undoubtedly due to the advantages gained by the low cervical incision and the routine use of prostigmin or pitressin immediately postoperatively.

*Retained Placenta, Lochiometra.*—It is of interest to note that abdominal section does not preclude the possibility of retained secundines. These patients bled postoperatively and suffered temperatures up to 104° F. Relief occurred when placental tissue was passed or removed through the cervix. Greater attention would have saved this complication.

*Disruption of Previous Cesarean Scar.*—In two repeat sections, the previous uterine scar had separated so that only the membranes kept the baby from the peritoneal cavity. Both of these patients had been previously sectioned for eclampsia by the classic routine, and both were extremely edematous at the time of that section. This may have been a factor in the poor healing of their incisions. Inasmuch as 2 out of 12 repeat sections showed disrupted scars, we feel that decision to deliver per vaginam after previous section is not to be taken too lightly.

lower morbidity and mortality figures in the potentially infected cases, but its indications can be and are pushed far beyond the limits of safety. The true extraperitoneal approach should and will supplant the low cervical section in this type of case.

The general surgeon or obstetrician who cannot bring to the operating table the skill and judgment necessary to perform the various types of extraperitoneal section carries a distinct hazard to his hospital and should be excluded from this particular branch of surgery.

The general practitioner or general surgeon with little or no obstetric training is not particularly qualified to evaluate the dystotic pelvis. All decisions to perform such operations should be made in consultation with a skilled obstetric specialist.

The obstetrician who does not adequately prepare in advance for the eventuality of shock and hemorrhage in cesarean section likewise contributes to the too high mortality for this operation.

Finally, the general practitioner, who does not approach each obstetric problem with respect and with the thought of possible abdominal delivery and who by needless interference and haphazard judgment jeopardizes the safety of that operation, has likewise been remiss in his duty to his patient.

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## A METHOD FOR REDUCING THE SIZE OF THE UTERUS IN VAGINAL HYSTERECTOMY\*

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VAGINAL hysterectomy may be performed by any one of many techniques. A large uterus is usually reduced in size by splitting in two or by morcellation and then removing it piecemeal. In the course of these procedures, it was found that amputating the cervix facilitated the turning of the corpus. Also in a large corpus (i.e., multiple fibroids), it was found that a good part of the corpus could be coned out with the cervix. However, there was the danger of opening an infected cervix or opening the uterine cavity in which a carcinoma might be present. Since carcinoma of the corpus or isthmus of the uterus may be associated with fibroids (0.5 to 4.4 per cent, according to different observers; 10 per cent over the age of 50 according to Bland-Sutton), I developed a procedure to decrease the size of the uterus without opening the cervical canal or the cavity of the corpus. The new procedure is helpful not only for a large uterus but also for carcinoma of the corpus or isthmus associated with fibroids and in unsuspected chronic pyometra secondary to stricture of the cervix.

In a consideration of the technique of vaginal hysterectomy, it is of interest to relate its historical development. No mention of vaginal hysterectomy was made in

\*Presented at a meeting of the Chicago Gynecological Society, March 21, 1941.

Table VIII reveals the par toward which smaller hospitals must strive. The statistics of the large obstetric clinics are admirable. In all fairness, it must be realized that the dilution caused by the large number of repeat sections (28 per cent of clean, elective cases) contributes to the excellence of their final statistics. The mortality at Mount Vernon Hospital for the past five years has dropped to 3.7 per cent and with no fatality for the last 50 cases.

TABLE VIII. COMPARATIVE MORTALITY STATISTICS

SOURCE	NO. DELIVERIES	NO. SECTIONS	PER CENT OF SECTIONS	PER CENT OF MATERNAL MORTALITY
National before 1931	262,852	2,289	0.77	9.45
National 1931-1939	782,718	15,768	2.55	4.69
Chicago Lying-in 1930-1939	18,009	1,000	5.5	0.8
New York Lying-in	5,456	153	2.8	0.65
Mount Vernon, New York	8,459	204	2.6	5.1

TABLE IX. FETAL MORTALITY, 1936-1940

Deaths—10 9%

Stillborn

(a) 5 pound premature with abruptio placentae and Porro

(b) 3 pound premature in fulminating eclampsia

Neonatal—8

(a) Three monsters, anencephaly with megalofetus, breech with hydrocephaly, congenital heart with absence of abdominal wall.

(b) Two prematures with placenta previa

(c) Two atelectatic aspiration pneumonias

(d) One premature in nephritic mother

Table IX reviews the fetal mortality. In the hemorrhagic and toxemic group, the life of the mother was at stake and section was elected in spite of the evident prematurity of the fetus. The aspiration deaths were probably preventable. We have, in recent months, instituted a definite resuscitation team. The two monster deaths were due to error in judgment. Both sections were done in the interest of the fetus. The fetal heart was irregular before labor, and it was assumed that there was cord compression. The irregularity proved to be due to congenital anomaly and not due to fetal distress.

#### SUMMARY

It is felt that any evaluation of the status of cesarean section is incomplete without the inclusion of statistics from the smaller community hospitals. Such a survey has herein been presented. It is likewise felt that it is more truly representative of general conditions than the surveys from the larger and leading obstetric centers. It is hoped that the natural local rivalry instigated by the publication of such surveys will inevitably tend to produce better results.

#### CONCLUSIONS

The most common causes of death in cesarean section still are peritonitis, shock, and hemorrhage. The treatment of dystocia after rupture of the membranes and trial labor by any form of transperitoneal section carries with it considerable risk. The low cervical section is a vast improvement over the older classic methods and will, undoubtedly,



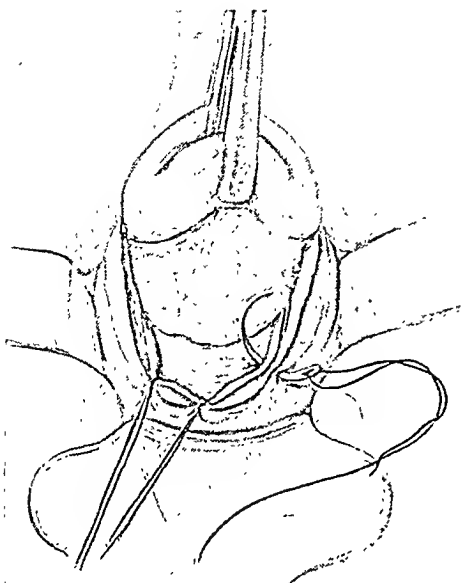


Fig. 1.

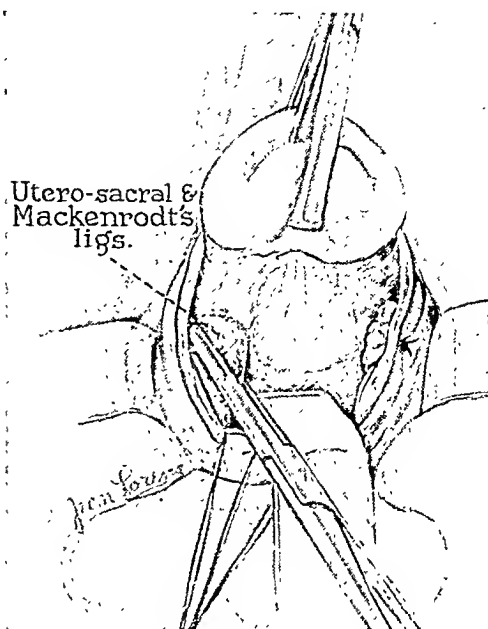


Fig. 2.

Fig. 1.—Modified vaginal hysterectomy: Posterior cul-de-sac has been opened and the posterior peritoneum is sutured to the posterior vaginal wall. The same procedure is carried out anteriorly, so that the anterior peritoneum is sutured to the anterior vaginal wall.

Fig. 2.—Modified vaginal hysterectomy: The uterosacral and the base of the Mackenrodt's ligaments are clamped, cut, and sutured to the lateral wall of the vaginal vault on each side.

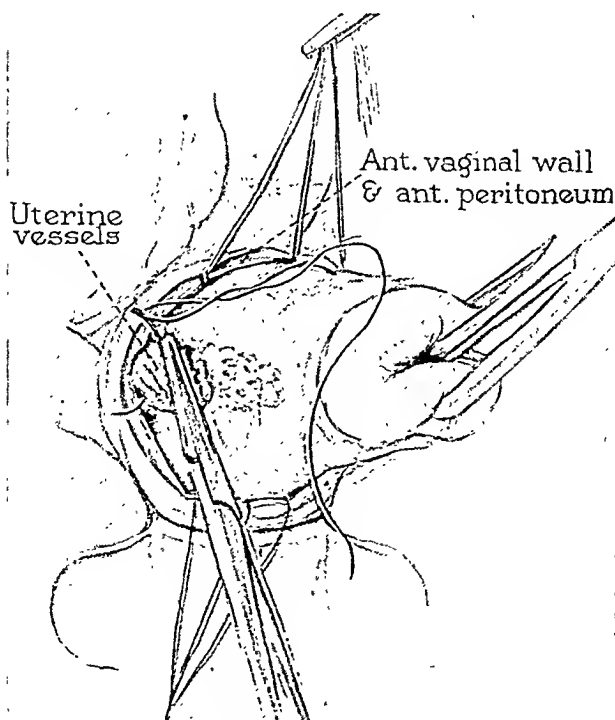


Fig. 3.—Modified vaginal hysterectomy: The bladder is retracted as well as the posterior peritoneum. The uterine vessels are clamped, cut, and ligated.

ancient gynecology until the time of Soranus who practiced in Rome from A.D. 98 to 138. He suggested that if part or all of the uterus became black, because it remained prolapsed for a considerable time, it should be resected partially or entirely. Paulus Aegineta (A.D. 625 to 696), who appeared to be the first professional man midwife, advocated the operation for irreducible inversion. The next reference to the operation was for ulcerated prolapse by Albucasis the Arabian (1073 to 1106). No details of the procedures were given. There is no mention of it during the Renaissance.

In the modern period, Andreas A. Cruce, of Granada, performed a hysterectomy in 1560 with a cautery iron for a carcinoma in a prolapsed uterus. This method was used for the treatment of carcinoma of the cervix for quite some time. In 1813 C. J. M. Langenbeck performed a vaginal hysterectomy by enucleating a carcinomatous prolapsed uterus without opening the peritoneum. Langenbeck published the first monograph on the subject in 1818. Following this work came Sauter's description of dividing the broad ligaments and performing a vaginal hysterectomy in 1822. Blundell in 1828 and Recamier in 1829 published their experiences. J. C. Warren in 1829 apparently did the first vaginal hysterectomy in America. Many failures followed, probably due to imperfect asepsis and lack of anesthetics. Only few cases were found in the literature until W. A. Freund in 1878 described his technique for vaginal hysterectomy. Freund's technique is still practiced today and has served as the basis for all modifications of vaginal hysterectomy. Czerny, Lieberman, Hegar, Kaltenbach, and Martin played an important part in developing the earlier technique. In the present century Kelly, Schuchardt, Schauta, Adler, and their followers are the main exponents. Doyen (1859-1916) who performed the operation by the use of clamps said, "No man can call himself a gynecologist until he can perform a vaginal hysterectomy," and "that the gynecologist shall be capable of applying as faultless a technique per vaginam as he would if performing per abdomen." Today Kennedy, of Philadelphia, still champions the clamp method advocated by Price.

#### AUTHOR'S TECHNIQUE OF VAGINAL HYSTERECTOMY

1. Usual preoperative preparation of 1 per cent iodine douche and soapsuds enema night before and morning of operation.

2. Morphine ( $\frac{1}{6}$  gr.) and scopolamine ( $\frac{1}{150}$  gr.) one and one-half hours and three-quarters of an hour before operation if no change in pulse (above 120) and respiration (below 12).

3. Anesthesia: ether, ethylene, cyclopropane or local (pudendal block and infiltration 1 per cent novocaine).

4. Lithotomy position; vaginal preparation of soap and water wash, iodination and catheterization. Buttocks four to six inches over edge of table.

5. Weighted speculum inserted into the vagina. Cervix grasped with two vulsella and firmly pulled down. Lateral retraction. 2.0 c.c. of pituitrin (S) injected into the cervix.

6. Circular incision around portio guided by estimate of position of bladder and depth of posterior cul-de-sac. Vaginal wall wiped back with gauze exposing anterior and posterior peritoneal reflections.

7. Posterior peritoneal sac is opened between uterosacral ligaments and sutured to the vaginal wall with three fine (0) catgut sutures which are kept long on a Koehler forceps (Fig. 1).

8. Each uterosacral and part of the paracervical ligaments are clamped, cut, and ligated (No. 2 chromic catgut), and then sutured into the adjacent vaginal wall (Fig. 2).

9. Anterior peritoneal sac is opened between bladder pillars and the edge is sutured to the vaginal wall with three fine (0) catgut sutures

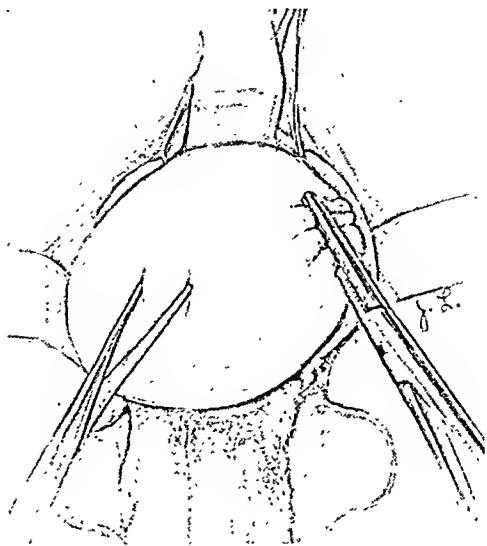


Fig. 5.—Modified vaginal hysterectomy: The remaining capsule of myometrium is brought forward exposing the tube, the round and uteroovarian ligaments, which are clamped on each side; the fundal capsule is removed; the tubes and ovaries are inspected. The uterine and cervical cavities are exposed by another person and the operator then inspects the cavities for carcinoma as the specimen is held up for his observation. If no carcinoma is found, the ligament stumps are ligated.

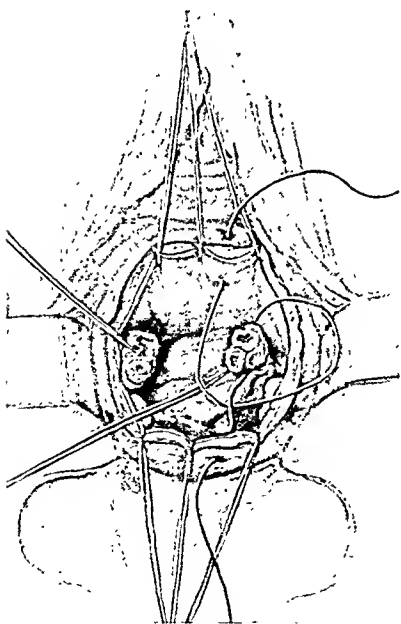


Fig. 6.

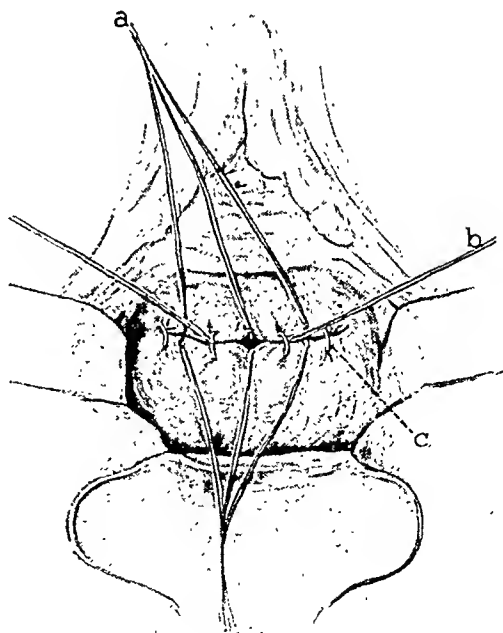


Fig. 7.

Fig. 6.—Modified vaginal hysterectomy: The ligament stumps are fixed in the midline of the vaginal vault, allowing only a small space between them. The stumps are, therefore, extraperitoneal, pulling up and supporting the central portion of the vagina and in most instances lengthening the vagina.

Fig. 7.—Modified vaginal hysterectomy: The lateral portions of the vault are closed with interrupted sutures. An iodoform gauze drain is inserted in the central opening of the vault. All sutures are now cut.

which are held long by a Koehler forceps. A long narrow retractor raises the bladder.

10. The uterine vessels are visualized, elamped, cut, and ligated on each side (No. 1 or 2 ehromic catgut). A long narrow retractor is inserted into the posterior cul-de-sac (Fig. 3).

11. An incision is started in the uterine wall just medially to the right uterine vessels and continued toward the left side and carried around. As the cervix is pulled down, the myometrium is cut so that the whole endometrial cavity with a thick layer of myometrium is removed with the cervix. Only the tubal lumina are traversed (Fig. 4).

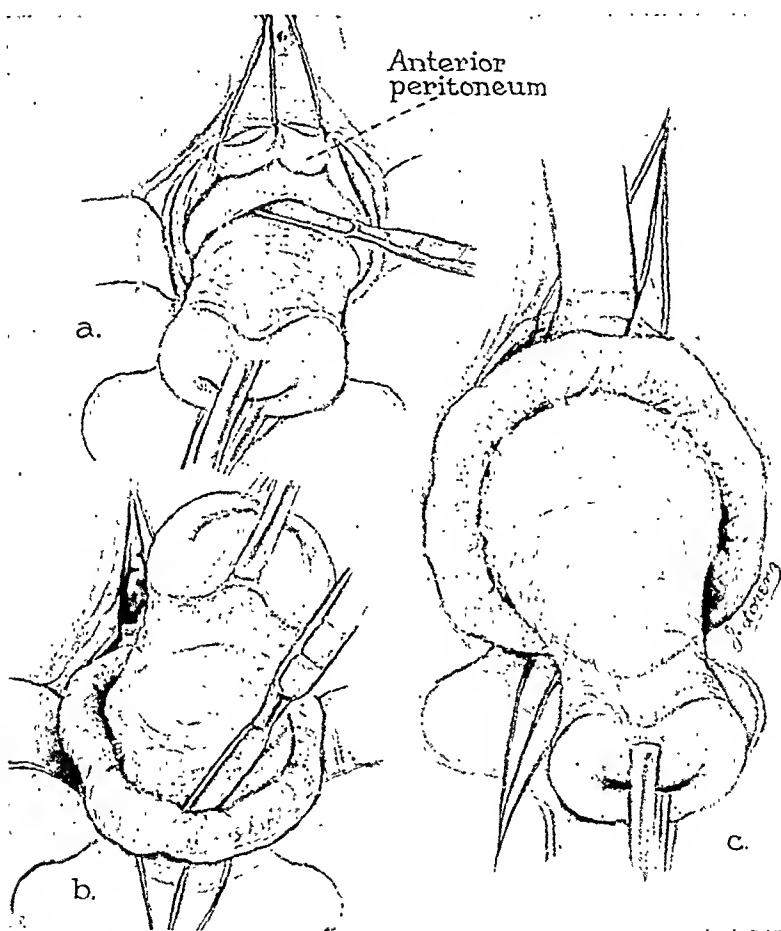


Fig. 4.—Modified vaginal hysterectomy: (a) The incision is now started medially to the point where the vessels have been ligated and encircles the cervix. (b) The cervix is pulled firmly downward and then upward as the major portion of the myometrium is shelled-out, leaving a capsule. (c) The major portion of the myometrium with its unopened endometrial cavity comes away.

12. The fundus is brought forward through the anterior cul-de-sac (Fig. 5), or if there are many fibroids, morecellation may be necessary. The round ligaments, tubes, and uteroovarian ligaments on both sides are elamped, cut and ligated with long No. 2 ehromic eatgut sutures which are held. The fundus is thus removed. The adnexa are inspected for possible pathology. The uterine and eervical eavities are opened by an interne or an unscrubbed nurse to allow the operator to inspect

The technique described by me adds to the advantages of vaginal hysterectomy by enabling one to remove large uteri, by preventing contamination of the peritoneal cavity, and by avoiding the spill of carcinomatous tissue from an unsuspected carcinoma of the uterus.

#### REFERENCES

- (1) *Datnow, M.*: Proc. Royal Soc. Med. 127: 761, 1934. (2) *Green-Armytage, F. B.*: J. Obst. & Gynaec. Brit. Emp. 46: 848, 1939. (3) *Kennedy, J. W.*: Practical Surgery of the Abdominal and Pelvic Regions, Philadelphia, 1934, F. A. Davis Company. (4) *Lynch, F. W., and Maxwell, A. F.*: Pelvic Neoplasms, New York, 1931, D. Appleton-Century Co. (5) *McKay, W. J. S.*: The History of Ancient Gynecology, London, 1901, Bailliere, Tyndall & Cox.

#### DISCUSSION

DR. N. SPROAT HEANEY.—In the case described in the film, this procedure seemed to facilitate the hysterectomy greatly as the operator was enabled thereby to exert continuous traction and remove the uterus more rapidly than if the usual technique of morcellation had been followed. For this purpose I believe that his method is of distinct advantage. I do not believe that it is of importance in avoiding contamination from a carcinomatous or infected endometrium, particularly in view of the fact that he did not exercise the common precaution of blocking the cervical canal by sutures or clamps to prevent a spill through the cervical opening. Pulling down continuously as he did, increases the chance of escape of any infected material that may be in the uterine cavity, through the cervical canal. I wonder how often Dr. Lash is able to remove a block of the uterus containing the endometrial cavity without entering the endometrial cavity, since in fibroids of any size the uterine cavity is so tortuous that its location cannot be determined.

DR. H. O. JONES.—Dr. Lash removes the endometrial cavity but he leaves a certain amount of endometrial tissue between the Fallopian tube and the cavity of the uterus. As we know from Sampson's work this tissue has a proliferative activity, and it seems to me that it would be very dangerous to leave that portion of the Fallopian tube in.

Like Dr. Heaney, I cannot see any advantage and I can see many disadvantages in the use of this procedure.

DR. FREDERICK H. FALLS.—Dr. Lash has not pointed out that a similar operation of this kind may save difficulty in certain vaginal hysterectomies which cannot be done in a routine manner because of certain complications which preceded the indication for the operation, such as pelvic inflammatory disease. We have done a number of operations with a technique similar to that described by Dr. Lash in patients who had had an interposition operation and in whom the uterus had begun to show fibroid or malignant degeneration. One of our chief concerns is to remove the uterus without injury to the bladder. We take out practically all of the myometrium and do an extraperitoneal vaginal hysterectomy. In another group of patients which special indications created we have done vaginal hysterectomies on uteri that have had previous ventral suspensions. We have used this same technique Dr. Lash has shown and then left a small portion attached to the abdominal wall.

To avoid contamination, instead of sewing the cervix we pull it down and with a cautery cook the interior of the uterus. By doing that we thoroughly sterilize the cavity of the uterus, and then we can do what we want with the uterus. I do not think it is good technique to put iodoform gauze through the cervix of the uterus.

DR. W. H. RUBOVITS.—I can see some definite advantages in the operation that Dr. Lash performs. There is a definite advantage to reducing the size of the large uterus which we formerly did, either by splitting the uterus in the midline and removing one-half of the uterus at a time or by some form of morcellation. I can see no better way than the operation Dr. Lash describes of cutting away a

the endometrium. If carcinoma is present, the adnexa are excised by clamping the infundibulopelvic ligament, cutting, and ligating. The round ligaments alone are then utilized for fixation into the vaginal vault. If there is no carcinoma in the uterus or pathology in the adnexa each tube with its broad ligament, the round and uteroovarian ligaments are ligated (No. 2 chromic catgut).

13. The anterior vaginal wall with its peritoneum is sutured to the posterior wall with its peritoneum including the ligaments (Fig. 6). The lateral parts of the vaginal wall are sutured with one or two interrupted No. 1 chromic catgut suture. Thus, the ligaments and vessel stumps are extraperitoneal (Fig. 7). An iodoform gauze is inserted partly into the small peritoneal opening between the ligament stumps. The gauze is allowed to remain in place for forty-eight hours.

14. Any anterior or posterior plastic repair may now be done in the usual way.

#### POSTOPERATIVE CARE

1. One thousand cubic centimeters of 10 per cent glucose in normal saline solution intravenously.

2. Morphine sulfate,  $\frac{1}{6}$  gr. as necessary for forty-eight hours, then codeine sulfate and luminal for pain.

3. Fluids after nausea.

4. Catheterize every eight hours, or if patient urinates in small amounts, catheterize for residual urine every twelve hours.

5. Soft diet on second day and then solid food is added as indicated. Oil retention enema on third night followed by warm tap water enema the following morning. Mineral oil is given twice a day.

6. Patient is out of bed on the eighth day, walks on the ninth and may go home on tenth or twelfth day.

#### COMPLICATIONS

Low grade infections in the vault of the vagina as indicated by fever and foul seropurulent vaginal discharge have been observed which have responded to low pressure antiseptic douches. No marked infection such as peritonitis or pelvic abscess and no postoperative hemorrhages either immediate or late have been observed. In the subsequent postoperative examination granulation tissue in the wound or rarely a prolapsed fimbriated end of a tube have been seen.

The advantages of vaginal hysterectomy are: First, less shock, because of less exposure of the peritoneal cavity, and shorter operating time; second, no opening or closing of the abdominal wall, especially in an obese individual; third, no abdominal sear with risk of ventral postoperative hernia or evisceration; fourth, opportunity to overcome cystocele, rectocele, or enterocele; fifth, postoperative care is simple; sixth, drainage is better; seventh, convalescence is rapid and, therefore, shorter hospitalization. The contraindications are: First, fixation of the uterus due to large fibroids (larger than twelve weeks' pregnancy); second, pelvic inflammatory disease or previous pelvic operations; third, malignant disease of the corpus uteri in nullipara; and fourth, necessity for abdominal exploration.

dystrophy, unassociated with adiposity, can be produced in female guinea pigs by small hypothalamic lesions, reaching the ventral surface of the brain at the level of and just behind the optic chiasma (Dey, Fisher, Berry and Ranson, 1940; Dey, 1941). Some of these guinea pigs have atrophic ovaries and genitalia; others have hypertrophic genitalia and ovaries containing many well-developed follicles but no corpora lutea, showing that ovulation has not occurred; still others have normal ovaries and genitalia, run regular cycles and ovulate, but will nearly always refuse to accept the male. Occasionally one of these animals will mate and become pregnant. Most of the animals which do become pregnant fail to deliver in a normal manner.

In the clinical literature one finds hints that sterility in apparently normal women, abortions occurring without obvious cause, dystocia due to uterine inertia, and the convulsions of true eclampsia may be caused by a disturbance in function and balance of the endocrine glands. As a result of observations made on female guinea pigs with lesions in the hypothalamus, a method has been found for attacking such problems experimentally.

#### METHOD

Electrolytic lesions were placed in the hypothalamus of each of 74 female guinea pigs by means of the Horsley-Clarke apparatus as described in previous publications (Dey, Fisher, Berry and Ranson, 1940; Dey, 1941). The lesions reached the ventral surface of the brain between the optic chiasma and the mammillary body. Virgins weighing 400 to 500 Gm. were used. They were divided into 2 groups. One group, 40 in number, was placed with males and the lesions were made either immediately after pregnancy was established or else at a later stage of pregnancy. A second group of 34 females had the lesions placed before they were mated.

The majority of the animals that were operated upon while pregnant soon aborted or else resorbed their fetuses. Twelve of the animals died. After termination of pregnancy by abortion, resorption or delivery, the 28 remaining animals were again placed with males and treated in exactly the same manner as the 34 which were operated upon while still virgin.

The operated animals were now divided into groups of 6 and a male was placed with each group. At frequent intervals the males were either rotated or else replaced by fresh males. The females were observed daily for signs of pregnancy. When it was definitely established that a female was pregnant, it was separated from the male.

Daily observations were made on the pregnant animals and the condition of the vaginal membranes recorded. Toward the end of pregnancy they were observed at more frequent intervals. At the first signs of parturition they were placed under continuous observation until the delivery had terminated.

At frequent intervals during the course of the experiment, the animals were placed in individual cages and the water intake was recorded. The animals were then classified according to the quantity of water that they consumed. Those that drank from 50 to 90 c.c. of water daily were considered as having a mild polydipsia; 90 to 150 c.c., a moderate polydipsia; and over 150 c.c., a severe polydipsia. The degree of polydipsia gave some indication of the extent of atrophy of the posterior lobe of the hypophysis. The atrophic lobe is deficient in both the antidiuretic and the oxytocic principles (Fisher, Ingram and Ranson, 1936; Fisher, Magoun and Ranson, 1938).

At the end of the experiment the animals were autopsied and the brains, hypophyses, and ovaries prepared for histologic study.

large portion of the uterus through the avascular area which will remove the endometrial cavity and a large block of the fibroid uterus.

DR. LASH (closing).—The suggestion of closing the cervix is an excellent one. I have tried to avoid the necessity of that by putting iodized gauze into the canal and using a volsellum. I do not use this operation in an infantile uterus, but in a large uterus. Whenever it is possible, the uterus is removed intact.

The reason we took out this uterus in the illustrated case, was that the patient, a 44-year-old woman, was bleeding and had multiple fibroids and large cystic ovaries.

It is true that we have to traverse the tubal cavity in removing the endometrial cavity, but we try to get the major portion of the myometrium in removing the myometrium with the endometrium. Two cubic centimeters of pituitrin will make the myometrium practically bloodless.

I would like to reiterate that this operation is not to be done on the normal uterus where the corpus can be removed in toto. It is the uterus the size of a twelve to fourteen weeks' pregnancy that should be removed this way. In certain instances, as Dr. Falls brought out, we can really remove the uterus in the presence of inflammatory disease where there are some adhesions present.

## DISTURBANCES IN PREGNANCY AND LABOR IN GUINEA PIGS WITH HYPOTHALAMIC LESIONS\*

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GNADOTROPIC hormones formed in the anterior lobe of the hypophysis are essential factors in the development of the Graafian follicles, in ovulation and in corpus luteum formation. Ovarian hormones in turn react upon the anterior pituitary. Without a proper balance of the pituitary follicle-stimulating and luteinizing hormones and the ovarian estrogenic and corpus luteum hormones pregnancy cannot occur. It is possible that the hypophysis may also influence pregnancy through its thyrotropic hormone and the thyroid gland. There is some evidence that the oxytocic hormone formed by the posterior lobe of the hypophysis may play a role in normal labor (Fisher, Magoun and Ranson, 1938).

The master gland, the hypophysis, lies close to the base of the brain to which it is attached by the infundibulum. The part of the brain to which it is attached is known as the hypothalamus. It forms the floor of the third ventricle immediately behind the optic chiasma. In recent years evidence has accumulated to show that the hypothalamus exerts an important control over the anterior as well as the posterior lobe of the hypophysis. The evidence showing that the hypothalamus influences the gonadotropic functions of the hypophysis has been reviewed by Brooks (1940).

Clinical neurologists recognize adiposogenital dystrophy as a sign of damage to the hypothalamus; but for obvious reasons it has not been possible to study this condition experimentally in man. The syndrome has been produced in dogs by injuring this part of the brain (Bailey and Bremer, 1921; Biggart and Alexander, 1939). Various types of genital

\*Aided by a grant from the Committee for Research in Problems of Sex, National Research Council.



*Animals Which Became Pregnant After Lesions Were Placed in the Hypothalamus.*—The 28 females, which survived the termination of pregnancy by resorption, abortion, or parturition, and the 34 that were operated upon while virgin, were placed with males. Only 13 of this entire group of 62 animals became pregnant, although they were kept with males for many weeks. The cause of this sterility has been discussed in other papers (Dey, Fisher, Berry and Ranson, 1940; Brookhart, Dey and Ranson, 1940, 1941; Dey, 1941).

Three of the 13 animals that did become pregnant delivered successfully after a gestation period of normal length. Two of these had a moderate polydipsia while the third had a severe polydipsia. One other delivered fetuses at term but both the mother and offspring died within two days after the delivery. The remaining 9 animals died either at term or shortly before term without delivering. Six of the animals died from disturbances which we shall refer to as convulsions. Two other animals died when not under observation, but from the condition of their bodies and of the cages, it is not unreasonable to assume that they died from similar convulsions.

These convulsions came on suddenly during the latter part of the gestation period. They occurred periodically and were characterized by weakness of the animal, generalized contractions of the skeletal muscles, running movements, gnashing of teeth, squealing and, finally, general prostration and death of the animal. Between seizures the extremities were quite spastic and muscular twitchings frequently occurred. The seizures varied in duration; and the frequency of their occurrence increased from the time of onset up until the time of the animal's death some three to twelve hours later.

The nature of these convulsions can be understood better by studying the protocol of one of the animals. This animal had a moderate polydipsia. It became pregnant and carried pregnancy until the forty-ninth day of gestation. On this day the animal appeared to be in good health during the routine morning examination. Five hours later, however, it was found lying on its side and it was undergoing vigorous convulsions. The vaginal membrane was closed and there were marked fetal movements. The convulsions when first observed occurred at intervals of approximately fifteen minutes. During the convulsions the animal would squeal and either gnash its teeth or else bite the wire netting of the cage. This activity resulted in severe lacerations of the gums and tongue and loosening of the teeth. The strong contractions of the abdominal muscles, the squealing and the apparent agony of the animal gave one the impression that the animal was bearing down in an attempt to expel the fetuses. The convulsions occurred more and more frequently until, some eight hours later, the interval between seizures was only about thirty seconds. At this time the respiration was slow and the temperature of the animal had fallen to 94.7° F. The animal died about nine hours after the onset of the disturbance. Marked fetal movements continued up until within several minutes of the animal's death.

The convulsions in this animal were similar to those in others of this group. It is interesting to note that at least 6 animals underwent con-

## RESULTS

*Animals Which Became Pregnant Before Lesions Were Placed in the Hypothalamus.*—Of the 40 animals in which the hypothalamic lesions were placed during pregnancy, 28 aborted or resorbed their fetuses and 12 retained pregnancy to term. The cause of the abortions has not been determined. Nineteen of the animals maintained pregnancy for four days or more and 11 of these for at least a week after the lesion had been made in the hypothalamus. This suggested that factors other than those arising as a direct result of the operation were responsible for the termination of pregnancy. To confirm this, two pregnant females were subjected to control operations which were similar in every detail to those performed upon the 40 animals of this group, except that electrodes were not inserted into the brain and no lesions were made. Both animals maintained pregnancy until term and delivered normally. Moreover, lesions were placed in the mammillary bodies of 2 other pregnant animals. These also maintained pregnancy until term.

The 12 operated animals that maintained pregnancy until term showed considerable variation in their ability to deliver. Three of them delivered normally after gestation periods which were of normal length. Two of these had a normal water intake while the third had a mild polydipsia. Five others were able to effect delivery after normal periods of gestation, although the mechanisms of parturition appear not to have been normal. Either the fetuses were born dead or else the mothers died a short time after the delivery of dead fetuses. Three of these animals had a mild polydipsia, one had a moderate polydipsia, and the fifth had a normal water intake.

Only 4 of the 12 animals showed disturbances of parturition as severe as those observed in cats with diabetes insipidus by Fisher, Magoun and Ranson (1938). One animal, which had a mild polydipsia, began to make bearing-down movements late in pregnancy. After these movements had continued for some time the animal went into a coma and died. At autopsy a mature fetus was found in utero. A second animal followed a course similar to that of the animal just described. When delivery was not effected after several days, however, the animal was killed and 2 mummified fetuses were found in utero. The animal had a mild polydipsia. The 2 remaining animals both effected delivery but not in a normal manner and several days late. One animal delivered a dead fetus on the seventy-third day of gestation and five days later delivered another dead fetus. The second animal delivered 1 dead and 2 mummified fetuses on the seventy-second day of gestation and four days later delivered another dead fetus. The first animal had a moderate polydipsia while the latter had a mild polydipsia. In contrast with these observations, Boling and co-workers (1939) have reported that the interval between the delivery of the first and last members of a litter of normal guinea pigs was less than thirty minutes in 79 out of 80 cases. The normal gestation period in the guinea pig varies in length between sixty-two and sixty-eight days.

arrived in the laboratory and were operated upon soon after their arrival. Eleven of these promptly aborted. Three of the 4 remaining animals maintained pregnancy until term and delivered normally. Each had a normal water intake. The fourth animal, which had a moderate polydipsia, attempted to deliver thirty days after the lesion had been placed in the hypothalamus. When the animal was first observed in labor, a partially delivered fetus was hanging from the vagina. The animal failed to complete the delivery during the following hour so the investigator removed the fetus by traction. Three days later, the animal was again observed bearing down. After seven hours of these movements the head of a second fetus was exposed. One-tenth grain of dried posterior pituitary in saline was injected intraperitoneally. The bearing-down movements increased in frequency and twenty-five minutes later the delivery was completed.

One of the animals that had delivered normally became pregnant again. It delivered 2 dead fetuses on the seventy-seventh day of pregnancy, and a third dead fetus the following afternoon.

Only 2 of the animals that aborted following the operation became pregnant again. One animal, which had a severe polydipsia, was observed making bearing-down movements on the seventy-eighth day of pregnancy. Three hours later the head of a fetus was exposed. Delivery was not completed one and one-half hours later so the fetus was removed by the investigator. The second animal, which had a mild polydipsia, delivered 2 fetuses normally.

Observations were also made on 2 guinea pigs which were operated upon as virgins and later became pregnant. These were the only ones to become pregnant out of 14 virgin females which received the lesions and were later kept for several months with males. One of these 2 delivered 1 dead fetus on the seventy-fourth day of pregnancy. The other died on the sixty-seventh day of pregnancy. Two mature fetuses were found in the uterus. The first animal had a mild polydipsia while the latter had a normal water intake.

#### DISCUSSION

We believe that the abortions which follow the placing of lesions in the hypothalamus of pregnant guinea pigs are caused by the damage to this part of the brain since control operations, similar in every respect except that the electrodes were not inserted into the brain or were inserted into the mammillary bodies did not cause abortion. But the chief interest lies in the abnormalities seen in the animals which retained their fetuses. If we count those animals twice which were observed during 2 pregnancies, there were 16 which became pregnant before the lesions were placed and 18 which became pregnant after the lesions. Out of the 16, pregnant before the lesion, 6 delivered normally, 5 died during delivery or delivered dead fetuses, and 5 had prolonged and difficult labors. Out of the 18 which became pregnant after the lesions had been placed, 4 delivered normally, 1 died following delivery, 4 died at or shortly before delivery (convulsions?), 3 had prolonged and difficult labors, and 6 died in convulsions shortly before term.

vulsions and died three days or more before parturition should have taken place. In a few animals the vaginal membranes opened and a bloody mucous discharge was extruded; in the others, the membranes remained closed throughout the entire procedure.

The fetuses appeared to be hyperactive, especially between successive convulsions. Their movements could both be seen and felt through the abdominal wall. These movements indicated that the fetuses were alive within a few hours of the death of the mother.

In spite of the vigorous activity of the animals during the convulsions, their temperatures fell to very low levels, in some cases so low that they could not be registered upon a rectal thermometer, i.e., to a point below 92° F. In order to determine if this fall in temperature preceded the convulsions, daily temperature readings were taken in one animal, the last of the series. At 9 A.M. on the day of death the rectal temperature of the animal was 102.3° F. which is within normal range for the guinea pig. The animal at that time appeared to be in good health; but at 5 P.M. it was found in convulsions. The temperature at this time was 97.8° F. From this observation, it is not possible to say whether the fall in temperature preceded the convulsions, but if so, the interval must have been very short. The observation serves to emphasize that the convulsions make their appearance suddenly in an apparently normal animal.

All except one of the animals that died of these convulsions had had diabetes insipidus as evidenced by a water intake that was considerably higher than that of the normal animal. This is of interest as indicating an atrophy of the posterior lobe of the hypophysis (Fisher, Ingram and Ranson, 1938).

At autopsy an incision was usually made in the abdominal wall and the uterus and the fetuses were lifted out. In several animals, however, the uterus and vagina were removed in toto. In each of these specimens it was found that the heads of 2 fetuses, one in either horn, were jammed tightly into the vaginal canal.

No differences could be detected between the ovaries of the animals of this group and those of normal animals which were killed on a corresponding day of pregnancy.

The hypothalami of the entire series of animals have been studied and described in a previous publication (Dey, 1941). The lesions in the animals which failed to become pregnant were bilateral, situated between the optic chiasma and the pre-mammillary nuclei, and they extended quite deeply into the hypothalamus. Those in the animals which became pregnant were similarly located but with the exception of 2 animals, they were either unilateral or else very superficially placed.

#### ADDITIONAL EXPERIMENTS

Since the work described in the preceding sections was completed we have had the opportunity to observe the effects of hypothalamic lesions on pregnancy and labor in 17 additional animals. All were young adults and the lesions were similar to those in the preceding experiments. Fifteen of the guinea pigs were pregnant when they

creased water intake but a few had shown a normal intake. On the other hand about half of those which delivered normally had shown increased water intake. It is, of course, possible that the oxytocic hormone might have been reduced below its effective level while the anti-diuretic hormone was still present in adequate amounts . . . but these experiments on the guinea pig can certainly not be offered as convincing evidence that the oxytocic hormone plays an essential part in labor.

The animals which became pregnant after lesions had been placed in the hypothalamus belonged to the group which ran regular sex-cycles following the operation and which must, therefore, have had a fairly normal secretion of pituitary gonadotropic and ovarian hormones. The hypophyses were not directly involved in the lesions. The ovaries were histologically normal. But, since many of the other guinea pigs with hypothalamic lesions showed clear evidence of abnormalities in ovarian and pituitary gonadotropic function, it is possible that those which became pregnant also had similar abnormalities of a degree insufficient to prevent breeding. The polydipsia shown by most of the animals is evidence that the antidiuretic hormone of the posterior lobe of the hypophysis was deficient in amount and this would indicate a probable deficit in oxytocin (Fisher, Ingram and Ranson, 1938). It is, therefore, difficult to avoid the suspicion that abnormalities in pituitary and ovarian hormones may have been responsible for the disturbances in pregnancy and labor described in this paper.

#### SUMMARY

Female guinea pigs with medially placed lesions in the hypothalamus, reaching the ventral surface of the brain at the level of and just behind the optic chiasma were usually sterile, although some did become pregnant. These usually had unilateral or very superficial lesions.

Slightly less than one-third of the pregnant guinea pigs with hypothalamic lesions delivered normally. About half of them had definitely prolonged or delayed labor or delivered dead fetuses. It was not possible to establish definitely a relationship between this dystocia and a deficit in oxytocic hormone, but it may be that such a relationship exists.

Six of the pregnant guinea pigs with hypothalamic lesions died in convulsions which appeared suddenly late in pregnancy and were rapidly fatal. These convulsions are of interest because of their resemblance to eclampsia.

#### REFERENCES

- Bailey, P., and Bremer, F.: *Arch. Int. Med.* 28: 773, 1921. Biggart, J. H., and Alexander, G. L.: *J. Path. & Bact.* 48: 405, 1939. Boling, J. L., Blandau, R. J., Wilson, J. G., and Young, W. C.: *Proc. Soc. Exper. Biol. & Med.* 42: 128, 1939. Brookhart, J. M., Dey, F. L., and Ranson, S. W.: *Proc. Soc. Exper. Biol. & Med.* 44: 61, 1940. *Idem*: *Endocrinology* 28: 561, 1941. Brooks, C. McC.: *Res. Publ. Ass. Nerv. Ment. Dis.* 20: 515, 1940. Dey, F. L.: *Am. J. Anat.* 69: 61, 1941. Dey, F. L., Fisher, C., Berry, C. M., and Ranson, S. W.: *Am. J. Physiol.* 129: 39, 1940. Fisher, C., Ingram, W. R., and Ranson, S. W.: *Diabetes Insipidus and the Neurohormonal Control of Water Balance*, Ann Arbor, 1938, Edwards Brothers. Fisher, C., Magoun, H. W., and Ranson, S. W.: *AM. J. OBST. & GYN.* 36: 1, 1938.

It should be noted that none of the animals which were pregnant when the lesions were placed developed convulsions, while at least 6 and probably 2 or 3 others which became pregnant after the operation died in convulsions which appeared suddenly late in pregnancy and were rapidly fatal. It is interesting to speculate on the relation of these convulsions to eclampsia. Although no satisfactory explanation can be given for the occurrence of these convulsions, it is possible that they may have resulted from a disturbed endocrine balance resulting from an alteration in pituitary hormones brought about by the hypothalamic lesion.

In a majority of the animals which went to term, there was obviously a serious disturbance in the mechanism of labor. Difficult and prolonged labor was observed in 7. Seven others which were not under such close observation died as a result of labor or delivered only dead fetuses. It is possible that in these also labor was unduly prolonged. In 6 of these 14 animals the onset of labor was definitely delayed, beginning on the seventy-second, seventy-third, seventy-fourth, seventy-seventh, seventy-eighth, and seventy-eighth days, respectively. As has already been stated, the normal gestation period for the guinea pig is sixty-two to sixty-eight days.

It is possible that the disturbances in parturition were due to a deficiency of the oxytocic hormone formed by the posterior lobe. Most of the lesions in the hypothalamus were so placed as to interrupt at least a part of the fibers of the supraopticohypophysial tract. It has been shown that when this tract is completely interrupted by hypothalamic lesions in cats the posterior lobe of the hypophysis undergoes atrophy, and its content of the antidiuretic, pressor, and oxytocic hormones is decreased almost to the vanishing point (Fisher, Ingram and Ranson, 1938). As a result of the loss of antidiuretic hormone, diabetes insipidus occurs. In this way diabetes insipidus was produced in 85 cats. This number included 7 that had had lesions placed in the hypothalamus during pregnancy. These 7 went to term, but had prolonged labors and all but one of them died. It was suggested that the dystocia might be due to deficiency of the oxytocic hormone, and the literature bearing on the significance of this hormone for labor was reviewed (Fisher, Magoun, and Ranson, 1938).

Whatever may have been the cause of the dystocia in these cats it is interesting that slightly less than  $\frac{1}{3}$  of the pregnant guinea pigs with similar hypothalamic lesions delivered normally. About half of them had definitely prolonged or delayed labor or delivered dead fetuses. These animals would seem to have had a disturbance essentially similar to that in the cat. The 6 guinea pigs that died in convulsions presented an entirely different clinical picture, but it is possible that the cause of the convulsions may have been in some way related to the cause of the dystocia in the other animals.

In the guinea pigs water exchange was measured only by the water consumed and the observations on diabetes insipidus were, therefore, less accurate than on the cat where both fluid intake and output were carefully measured. The majority of the guinea pigs which had prolonged or delayed labor or delivered dead fetuses had shown an in-

Luer syringe. The solution was injected into the antecubital vein. The rate of injection was governed by the individual response and according to the type of response desired. The usual injection time for 50 c.c. of the aqueous solution was two to three minutes. Caution should always be practiced, but seldom is there indication to alter the injection rate when the dose is only 1 c.c. of a 10 per cent solution per kilo of body weight.

In order to be able to make a more accurate evaluation of the effects of intravenous paraldehyde, no other drug was administered during the course of labor. An ether anesthetic was usually given at the time of delivery unless intravenous paraldehyde was being given as the general anesthetic.

Of the 100 patients, one group received a single intravenous injection of paraldehyde from ten minutes to nine hours before the time of delivery, and it is from this group that several blood paraldehyde curves were determined. The second and largest group received intravenous paraldehyde from three to thirty minutes prior to the administration of a rectal dose of paraldehyde. In the third group of patients, an attempt was made to use intravenous paraldehyde as a general anesthetic at the time of delivery.

#### BLOOD LEVELS FOLLOWING THE USE OF INTRAVENOUS PARALDEHYDE

According to Gardner and others,<sup>8</sup> it is usually necessary to produce a blood paraldehyde level of 15 to 20 mg. per 100 c.c. if amnesia is to be expected. After observing that most patients who received 1 c.c. of 10 per cent paraldehyde solution per kilogram of body weight experienced a period of complete amnesia, it was decided to determine the blood paraldehyde levels following the administration of this dose. The analytical method as described by Levine and Bodansky<sup>9</sup> was used. Blood samples were taken at 5-, 15-, 30-, 60-, and 120-minute periods. Referring to Fig. 1, one sees that the 5 curves are similar in each instance, and for this reason, further determinations were not thought to be indicated. The highest maximum blood level for the five individual curves was 22 mg. per 100 c.c., and the lowest maximum level for the group was 14.8 mg. per 100 c.c. One of this group of five patients failed to experience a definite period of complete amnesia. This patient's maximum blood paraldehyde concentration was 19.4 mg. per 100 c.c.

#### ANALYSIS OF RESULTS

Twenty-nine patients who received neither previous nor subsequent medication of any kind were given a single intravenous injection of paraldehyde from ten minutes to nine hours before delivery. In 23 of this group, delivery occurred within one hour and a half of the time of administration. Of this group of 29 patients, 17 received 0.7 c.c. of 10 per cent paraldehyde per kilo of body weight, and 12 received 1 c.c. of 10 per cent paraldehyde per kilo, the actual amount of 10 per cent solution varying from 36 to 79 c.c. Of the 17 patients who received 0.7 c.c. of 10 per cent paraldehyde per kilo of body weight, 8 experienced a period of complete amnesia, while the other 9 had fair to complete analgesia for a period of

## THE INTRAVENOUS ADMINISTRATION OF PARALDEHYDE DURING LABOR

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THE use of intravenous paraldehyde for obstetric analgesia and anesthesia has not, to our knowledge, been previously reported. With the purpose of determining the suitability of this method of administration this study was undertaken. We present our observations upon 100 patients who received intravenous paraldehyde during the course of labor.

Since the introduction of paraldehyde as an obstetric analgesic by Rosenfield and Davidoff<sup>1</sup> in 1932, the popularity of this drug has steadily increased. Its comparative safety for both mother and child is becoming more widely recognized. Though paraldehyde is usually administered by the rectal or oral route, parenteral use has been advocated from time to time for various purposes. Johnson<sup>2</sup> has administered paraldehyde parenterally for the control of pain and convulsive states. One of his patients received 60 c.c. of paraldehyde by intramuscular injection over a period of twenty-four hours with no harmful effects. The disadvantage of the intramuscular route is that severe burning and local irritation immediately result, though Johnson observed no cases of muscle necrosis. Intravenous paraldehyde was first used by Noel and Souttar<sup>3</sup> in 1912 as a hypnotic, analgesic, and anesthetic agent. Robinson<sup>4</sup> recommended intravenous paraldehyde for the production of narcosis in the performance of pneumoencephalography. His maximum single dose was approximately 0.4 c.c. per kilogram of body weight. Basing his work on animal experimentation, Beauchemin and others<sup>5</sup> calculated the lethal dose for a 150-pound man to be 40 to 60 c.c. if the paraldehyde was given intravenously. Caldwell<sup>6</sup> used comparatively small doses of intravenous paraldehyde (1 to 3 c.c.) to control satisfactorily the convulsions of eclampsia. Paraldehyde is commonly stated to be the least toxic of the hypnotic drugs.<sup>7</sup>

### PREPARATION AND ADMINISTRATION

For intravenous use an aqueous solution of paraldehyde is much to be preferred to the undiluted drug, since the latter causes spasms of coughing. The assumption that this reaction may result from lung irritation produced by small emboli of undissolved paraldehyde, is suggested by the fact that paraldehyde is rather slowly soluble. At any rate we know that this reaction may be eliminated entirely by dissolving the paraldehyde in water. Paraldehyde is soluble to the extent of one part paraldehyde to nine parts of water at room temperature. One hundred cubic centimeters of the 10 per cent solution, made by adding 10 c.c. of paraldehyde to 90 c.c. of sterile distilled water, usually suffices. Fresh solutions were prepared shortly before the time of intravenous administration, using paraldehyde of the same U.S.P. quality as is used for oral and rectal administration. Since comparatively large volumes of the aqueous solution are required, it is necessary to use a 50 c.c.



per cent paraldehyde solution per kilo of body weight, only three remembered getting the rectal dose. It was hoped that the intravenous paraldehyde would aid the patient in retaining the rectal dose, but we found that approximately 40 per cent of the patients expelled all or part of it. Of the 35 patients who retained all of the rectal medication, 31 experienced complete amnesia for the remaining course of labor, while the other 4 experienced partial amnesia and marked analgesia. The average duration of labor for these 58 patients, most of whom were primiparas, after the intravenous paraldehyde injection, was four hours and fifty-three minutes. We found that by the use of this combination of intravenous and rectal paraldehyde, amnesia and analgesia may be produced from the moment the intravenous paraldehyde is injected.

The third group of 14 patients were given intravenous paraldehyde at the time of delivery as a general anesthetic (Table I). Patient 1, a para i, had a funnel

TABLE I. PERTINENT DATA OF 14 PATIENTS RECEIVING INTRAVENOUS PARALDEHYDE DURING DELIVERY

PATIENT	DOSE C.C. OF 10% AQUEOUS PARALDEHYDE	DOSAGE C.C./KILO	DURATION OF ANES- THESIA BEFORE DELIVERY MINUTES	AMNESIA	ANALGESIA
1	125	0.260	30	Complete	Complete
2	71	0.100	20	Complete	Complete
3	80	0.114	15	Complete	Complete
4	84	0.100	20	Complete	Complete
5	100	0.133	20	Complete	Complete
6	50	0.070	5	Complete	Complete
7	150	0.200	20 minutes and dur- ing repair of episiotomy	Complete	Complete
8	90	0.136	25	Complete for pain	Complete
9	100	0.142	15	Complete	Complete
10	94	0.140	15	Partial	Marked
11	46	0.070	12	Partial	Marked
12	100	0.146	20	None	Marked
13	58	0.070	8	None	Marked
14	50	0.070	15	None	Marked

pelvis and was delivered by low forceps. Patient 2 had a temperature of 103.2° F. at the time of delivery, and eight hours before delivery the fetus had died in utero. Patient 6, was a severe pre-eclamptic who delivered a macerated fetus; in addition to her intravenous paraldehyde she had received 14 c.c. of paraldehyde per rectum eight hours before delivery. Patient 7, a primipara, had received 7.1 c.c. of the intravenous paraldehyde and 30 c.c. of paraldehyde per rectum six hours before delivery. At the time of delivery this patient received an additional intravenous injection of 15 c.c. of the 10 per cent aqueous paraldehyde solution while forceps were being applied and the episiotomy repaired. This patient was never sufficiently controlled to repair the episiotomy satisfactorily, although she showed signs of deep anesthesia, as evidenced by tongue swallowing and loss of pharyngeal and corneal reflexes. Patient 8, a primipara, was delivered by low forceps and episiotomy, the episiotomy site being injected with novocaine. Patients 3, 4, 5, 9, 10, 11, 12, 13, and 14 were all normal multiparas who delivered spontaneously. Of the entire group of 14 patients, 9 experienced complete amnesia for pain, while 7 had amnesia for all events. All patients agreed that the pain was lessened.

*Reactions.*—In this group of 100 patients we failed to observe any untoward reactions to the intravenous paraldehyde. In 44 per cent of the patients more or less arm pain was produced during the time of injection. The pain characteristically follows the course of the veins. Some patients felt pain as high as the subclavian veins. This arm pain may be practically eliminated by elevating the arm during the

from thirty to sixty minutes. Of the 12 patients who received 1 c.c. of 10 per cent paraldehyde per kilo, 10 experienced a period of complete amnesia for twenty to ninety minutes, while the other 2 patients had good analgesia. The majority of these 29 patients were multiparas in whom delivery was imminent, and it is likely that it is under these circumstances that intravenous paraldehyde will find its greatest field of usefulness. The screaming multipara who is reaching the end of her toil can be rapidly and effectively calmed with intravenous paraldehyde.

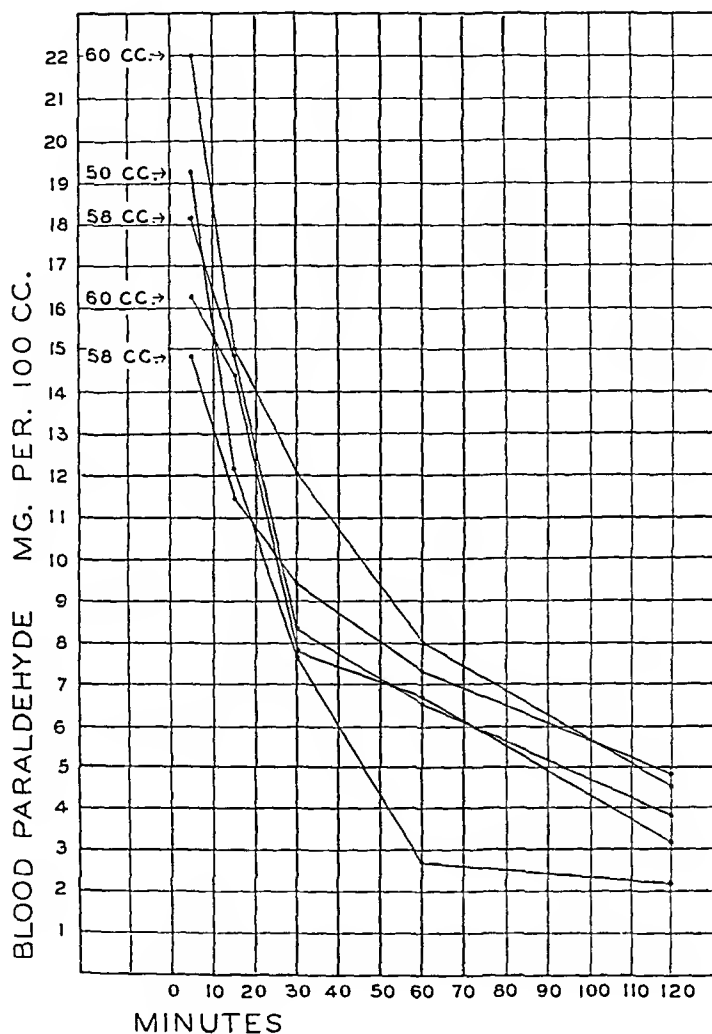


Fig. 1.—Blood paraldehyde concentrations following intravenous administration of 1 c.c. of 10 per cent solution per kilogram body weight. Figures at top of each curve represent the dose administered in cubic centimeters of 10 per cent aqueous solution.

The second and largest group consisted of 58 patients who received intravenous paraldehyde in conjunction with rectal paraldehyde in olive oil. Of these, 25 received 0.7 c.c. of 10 per cent aqueous solution per kilo of body weight and 33 received 1 c.c. of 10 per cent solution per kilo, the actual dose varying from 40 to 82 c.c. The rectal dose was 0.4 c.c. of undiluted paraldehyde per kilo, the actual amount varying from 20 to 36 c.c. The interval elapsing between the intravenous and rectal dose varied from three to thirty minutes, all but 4 patients receiving the rectal paraldehyde within twenty minutes after the intravenous paraldehyde. Of these 58 patients, 14 remembered the administration of the rectal paraldehyde, and most of these 14 patients had received the smaller intravenous dose of 0.7 c.c. of 10 per cent solution per kilo administered more than ten minutes before the rectal dose was given. In the group of 33 patients who received intravenously 1 c.c. of 10

received 1 c.c. of 10 per cent paraldehyde per kilo, only 3 remembered receiving the rectal drug.

4. Intravenous paraldehyde was used as an anesthetic for delivery in 14 patients. The minimum dose was 0.7 c.c. of 10 per cent paraldehyde and the maximum dose was 2.6 c.c. of 10 per cent paraldehyde per kilo. Only the larger doses of 1 to 2 c.c. of 10 per cent paraldehyde per kilo may be expected to produce complete analgesia and amnesia during the second stage of labor.

5. In no instance was a serious reaction encountered. Arm pain was experienced by 44 per cent of the patients during the course of injection. A mild coughing seizure occurred in 2 per cent and hiccoughs in 6 per cent.

6. Respiration and blood pressure are not essentially altered with the usual dose of 1 c.c. of 10 per cent paraldehyde per kilo, but with much larger doses, labored respiration may be encountered. The pulse rate was accelerated in 54 per cent, it not being uncommon to see an immediate increase of 20 to 30 beats per minute.

7. There is no evidence that intravenous paraldehyde produces any effect upon the infant.

8. The highest maximum concentration of blood paraldehyde as seen in 5 patients who received 1 c.c. of 10 per cent solution per kilo was 22 mg. per 100 c.c.

9. The beginning effect of intravenous paraldehyde is noted in ten to twenty seconds after the injection is started.

### CONCLUSIONS

Paraldehyde, in 10 per cent solution, dosage as outlined above, may be safely employed intravenously during labor without deleterious effect upon infant or mother.

Whereas, we do not recommend routine intravenous administration of paraldehyde during labor, we do feel that this method has a definite field of usefulness, under circumstances in which rapidly effective analgesia, of brief duration, is indicated.

The blood analyses in this study were done in the Maternal and Child Health Laboratories under the direction of Dr. V. M. Wilder.

### REFERENCES

- (1) *Rosenfield, H. H., and Davidoff, R. B.*: New England J. Med. 207: 366, 1932.
- (2) *Johnson, Allen S.*: Ibid. 210: 1065, 1934.
- (3) *Noel, H. L. C., and Souttar, H. S.*: Lancet 2: 818, 1912.
- (4) *Robinson, Leon J.*: New England J. Med. 219: 114, 1938.
- (5) *Beauchemin, J. A., Springer, R. G., and Elliot, G. A.*: M. Times & Long Island Med. J. 63: 179, 1935.
- (6) *Caldwell, Wm. Edgar*: N. Y. State J. Med. 26: 57, 1926.
- (7) *Miller, A. H.*: Anesth. & Analg. 15: 14, 1936.
- (8) *Gardner, Herman L., Levine, Harry, and Bodansky, Meyer*: AM. J. OBST. & GYNEC. 40: 435, 1940.
- (9) *Levine, Harry, and Bodansky, Meyer*: J. Biol. Chem. 133: 193, 1940.

course of injection. Six per cent of the patients developed a mild hiccough which lasted only a few minutes. Vomiting occurred in 3 per cent of the patients within a few minutes after intravenous paraldehyde. As all of these patients were in active labor, the vomiting could not be definitely attributed to the paraldehyde. Mild coughing seizures, probably due to incomplete solution of the paraldehyde in water, occurred immediately in two of the patients.

*Pulse.*—The pulse was counted immediately before and after the intravenous injection of paraldehyde. Fifty-four per cent showed a rise in pulse rate of from 2 to 40 beats per minute. It is not uncommon to see the pulse rate jump 20 to 30 beats during the course of injection. Twenty-five per cent of the patients had a slowing of the pulse rate. The change in this direction is less marked, the fall usually not amounting to more than 10 beats per minute. Twenty-one per cent showed no change in pulse rate.

*Blood Pressure.*—Neither systolic nor diastolic pressures showed any alteration of consequence. Forty-eight per cent showed a rise, 32 per cent a fall, and 20 per cent showed no change.

*Respirations.*—With the usual dose of 1 c.c. of 10 per cent paraldehyde per kilo there is usually little or no change in the respiratory rate, but when much larger doses are administered a definite stimulative effect is seen. The rate may be accelerated to 30 or 40 per minute, and the depth increased as was observed in several patients who received relatively large doses. For example, one patient was given 15 c.c. of intravenous paraldehyde at the time of delivery after having had rectal paraldehyde previously. We interpreted this labored respiration as an indication of overdosage.

*Patient's Conduct.*—As with all forms of narcosis, the actions of the patient are unpredictable. Sleep between pains was invariably produced with the 1 c.c. of 10 per cent paraldehyde per kilo dose.

*Effect Upon Fetus.*—The rate of the fetal heart showed no significant change. Some degree of apnea was noted in 6 infants, but never to a dangerous degree. Two of these infants were showing signs of distress before delivery as indicated by the passage of meconium. The uncorrected fetal mortality was 4 per cent. Two macerated infants were born of toxemic mothers. One infant died eight hours before the administration of intravenous paraldehyde. The fourth infant was ten weeks premature and died in forty-eight hours from intracranial hemorrhage. Obviously the intravenous paraldehyde was in no way a causative factor in these fetal deaths.

*Contraindications.*—During this study no patients were encountered in whom it was thought that intravenous paraldehyde was contraindicated. Nine of the patients were considered pre-eclamptic, 1 had chronic nephritis, 2 had rheumatic heart disease, 1 had epilepsy, and 1 had a temperature of 103.2° F. from an unknown cause.

#### SUMMARY

1. One hundred patients were given intravenous paraldehyde during the course of labor. The dosage varied from 0.7 to 1 c.c. of 10 per cent solution per kilo of body weight, the actual amounts varying from 36 to 150 c.c. of 10 per cent paraldehyde for a single injection.

2. Twelve patients received 1 c.c. of 10 per cent paraldehyde per kilo during the course of active labor, and 10 of these experienced a period of complete amnesia of usually less than one hour. Seventeen patients received 0.7 c.c. of 10 per cent paraldehyde per kilo during the course of active labor, and, of these, 8 experienced a period of complete amnesia.

3. Fifty-eight patients received intravenous paraldehyde from three to thirty minutes before a rectal dose of paraldehyde. Of the 43 who

tion by manipulative means. On the other hand, the fact that a functional disturbance of the cervix, such as cervical spasm, may be a cause of dystocia, has been recognized by many workers<sup>4-7</sup> and recently commented upon by de Oliveria Sarmiento.<sup>8</sup>

In a search for a preparation which would minimize the risk of childbirth by shortening labor, without introducing any new elements of danger, the nonnarcotic antispasmodic, syntropan\* was selected for trial. This is the phosphate salt of the tropic acid ester of 3-diethyl-amino-2, 2-dimethyl propanol. The drug has been demonstrated to have a definite antispasmodic action on spastic smooth muscle, due jointly to inhibition of the parasympathetic innervation and to direct relaxing action on the muscle cell.<sup>6-11</sup> The antispasmodic action is similar to that of atropine, but is not attended by the latter's undesirable by-effects.<sup>12, 13</sup>

Although the exact mechanism of the effect of syntropan on labor must await further physiologic and pharmacologic experiment, its relaxing effect on the uterine cervix would seem to be the rationâle for its efficacy in hastening cervical dilatation, thus shortening the duration of labor. Syntropan has been used in obstetrics by several investigators.<sup>5-7, 14</sup>

The principle of antispasmodic treatment would seem to be removal of resistance offered by the spastic cervix, at the same time preventing increase in rhythmic contraction and tension in the uterus as a whole which would normally be engendered by cervical resistance. Ivy and Rudolph<sup>15</sup> have pointed out that the uterus during labor is subdivided anatomically and physiologically into upper and lower segments between which a distinct functional difference may be observed. Spasm of the lower uterine segment (including the cervix), sometimes referred to as a hyperkinetic cervix, may result from nervous influences such as fear and anxiety. The familiar "constriction ring dystocia" may also occur, and is a condition which logically could be expected to respond to an antispasmodic drug.

#### METHOD

Our procedure consisted of the oral administration of two tablets of syntropan, 50 mg. each, to an experimental group of 34 patients when cervical dilatation of several centimeters was first noted. No other medication of any kind was given. This series of patients included both primiparas and multiparas. The progress of labor was closely observed in the experimental group and in a comparable number of untreated cases constituting the control group. Patients in both groups were taken at random and not selected according to their obstetric histories. The results, i.e., effect upon duration of labor, are given in tabular form (Tables I and II). There was a dramatic reduction of labor-time in the syntropan-treated cases.

TABLE I. PATIENTS TREATED WITH SYNTROPAN

	NUMBER OF PATIENTS	FIRST STAGE	AVERAGE DURA- TION OF LABOR		TOTAL	AVERAGE WEIGHT OF INFANT AT BIRTH IN POUNDS
			SECOND STAGE	THIRD STAGE		
Primiparas	14	5 hr. 20 min.	23 min.	10 min.	5 hr. 53 min.	7½
Multiparas	20	5 hr. 20 min.	25 min.	11 min.	5 hr. 56 min.	8½

\*Supplied by Hoffmann-La Roche, Inc., Nutley, New Jersey.

## THE SHORTENING OF LABOR WITH SYNTROPAN\*

JOHN E. STOLL, M.D., F.A.C.S., CHICAGO, ILL.

THE duration of labor,<sup>1</sup> usually conceded to be about eighteen hours in the primipara and about twelve hours in the multipara, has ever been an important consideration in obstetrics, in that many of the difficulties arising during and after delivery have their origin directly or indirectly in long labor. A material and harmless shortening of the parturition process, particularly the first stage, seemingly should result in the elimination of certain frequently encountered obstetric complications. Some of the complications which might be obviated include: uterine inertia; infection; deleterious effect on mother, particularly in the presence of cardiac disease, renal damage, or pulmonary tuberculosis; and finally a deleterious effect on the child.

These are but a few of the many dangers associated with prolonged labor. If we consider as well that the patient would be spared much of the pain and other incidental discomforts, all the advantages of harmlessly shortening the parturition process become obvious.

It is not surprising that numerous obstetricians have interested themselves in the problem of shortening the duration of labor and that various methods of doing so have been advocated. Certain of these may be mentioned, only to be condemned.<sup>2, 3</sup>

The undesirability of long-continued administration of the usual obstetric analgesics is well recognized. One of the pitfalls from over-enthusiasm in this direction, and one which certainly should be avoided, is depression or abolition of the so-called protective reflexes, as for example the pharyngeal reflex. Interference with this particular mechanism, alone, may have grave consequences.

An inquiry into the etiology of prolonged labor or dystocia will serve very well in introducing the treatment which is the subject of this report. The causes of dystocia are many, and are commonly classified as fetal and maternal. Further remarks on the former type, i.e., that which is due to the shape, size, and position of the fetus is not germane to this discussion. Neither are we directly concerned with pelvic dystocia or with difficult labor brought about by a disproportion between the size of the baby and the dimensions of the birth canal. As common, if not more so than the varieties already mentioned, is the condition known as cervical dystocia, which may be a manifestation of any one of several types of abnormal mechanisms, or a combination of abnormal mechanism plus other factors. There is, for instance, that common abnormality where incarceration of the anterior lip of the cervix delays or prevents descent of the presenting part. Such a condition from the very nature of the mechanics involved, requires correc-

\*Read at a meeting of the Chicago Gynecological Society, March 21, 1941.

in 3 cases, "cyanotic" in 1 case, and "stillborn" in 1 case. The average birth weight of the infants in this series was seven and one-fourth pounds, well within the normal range, hence weight of the infant can be eliminated as a factor which might otherwise have abnormally influenced duration of labor in the series as a whole.

#### SUMMARY

1. The rationale of the use of syntropan in labor is discussed.
2. The effect of the drug on labor-time in a series of 34 cases is demonstrated by comparison with the labor-time in a series of 26 untreated cases.
3. The effect of syntropan on the duration of labor in an additional group of 102 patients is also recorded.
4. The findings indicate that syntropan materially shortens labor.

#### REFERENCES

- (1) *Williams*: Obstetrics, ed. 4, New York, 1919. D. Appleton-Appleton Co., p. 250. (2) *Hillis*: Am. J. Surg. 48: 126, 1940. (3) *Waegeli*: Rev. méd. de la Suisse Rom. 58: 827, 1933. (4) *Kreis*: J. Obst. & Gynaec. Brit. Emp. 41: 955, 1934. (5) *Pschyrombel*: Med. Klin. No. 48, p. 1599, 1934. (6) *Peine*: Therap. d. Gegenw. 7: 333, 1935. (7) *Hirsch*: Brit. M. J. No. 4001, p. 559, 1937. (8) *de Oliveria Sarmiento*: An. bras. de ginec. 9: 411, 1940. (9) *Jung, Pierre, and Madelenat*: Compt. rend. Soc. d. Biol. 117: 929, 1934. (10) *v. Issekutz, Leinzinger, and v. Issekutz*: Arch. f. Exper. Path. u. Pharmacol. 176: 8, 1934. (11) *Fromherz*: J. Pharmacol. & Exper. Therap. 60: 1, 1937. (12) *Clark and Shires*: J. Pharmacol. & Exper. Therap. 63: 5, 1938. (13) *Yosida*: Folia Pharmacol., Japon (Brev.) 26: 103, 1939. (14) *Gamstaetter*: Muenchen med. Wchnschr. 82: 1491, 1935. (15) *Ivy and Rudolph*: Surg., Gynec. & Obst. 67: 188, 1938.

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#### DISCUSSION

DR. DAVID S. HILLIS.—Various efforts to shorten labor have often been the source of injury to mothers and babies. As a rule the effort is made to shorten labor more for convenience than for any justifiable reason. On this account a discussion of this question is undertaken with some hesitation.

Some months ago, our attention was called to the work that Dr. Stoll has just reported, and we undertook to study the effect of syntropan on the duration of labor in Cook County Hospital. A report of the results of this study on 600 cases will be made in due time. It may be said now that no serious objections were found to this method. The average length of labor with syntropan was shorter than without syntropan. The number of prolonged labors among the syntropan cases was greater than among the controls. In short, our experiences correspond quite closely with that which Dr. Stoll reported this evening.

DR. H. C. HESSELTINE.—It would be a real contribution if we could do something that would dependably shorten labor and yet do so with safety for both the mother and the baby. Many promising methods have come and finally disappear, either by formal retraction in the literature or through general discard, because they either did not work out or the earlier observations have not been sufficiently well controlled.

Some time ago Adair and Dieckmann, while making a special metabolic study on gravid patients, found that the duration of labor in primiparas was fifteen hours, while their control cases had a labor of thirteen hours. This difference is within the experimental range. The multiparas likewise in both the treated and control series had appreciably shorter labor than the textbook averages. Thus, it is evident that the length of labor may need to be re-established for each individual study because of possible special local factors, such as type of patient, obstetric procedures, technique, etc.

TABLE II. CONTROL PATIENTS

	NUMBER OF PATIENTS	FIRST STAGE	AVERAGE DURA- TION OF LABOR		TOTAL	AVERAGE WEIGHT OF INFANT AT BIRTH IN POUNDS
			SECOND STAGE	THIRD STAGE		
Primiparas	9	19 hr. 10 min.	3 hr. 35 min.	12 min.	22 hr. 57 min.	7
Multiparas	17	15 hr.	2 hr. 50 min.	11 min.	18 hr. 1 min.	8½

With the warranty of the encouraging results obtained in this small but convincing series of cases, the use of syntropan in the same manner was observed in a very much larger series of cases. The results in this larger series are recorded in Table III. The same dramatic reduction in labor-time was obtained, the first stage of labor averaging six hours and twenty-one minutes in 60 multiparous patients and nine hours and nine minutes in 42 primiparous patients.

TABLE III. PATIENTS TREATED WITH SYNTROPAN

	NUMBER OF PATIENTS	FIRST STAGE	AVERAGE DURA- TION OF LABOR		TOTAL	AVERAGE WEIGHT OF INFANT AT BIRTH IN POUNDS
			SECOND STAGE	THIRD STAGE		
Primiparas	42	9 hr. 9 min.	1 hr. 2 min.	7 min.	10 hr. 18 min.	7½
Multiparas	60	6 hr. 21 min.	29 min.	5 min.	6 hr. 45 min.	7½

## COMMENT

Upon comparing the labor-times of the control patients with those of treated patients, it can be seen that labor in the treated cases was, on an average, about one-half as long as in the control cases. Even in three cases in which version and extraction were done, the first stage of labor was definitely decreased in time.

In none of the treated cases was the duration of the second stage of labor longer than in the average normal; to the contrary, it was decidedly shorter. Thus it appears that the antispasmodic, syntropan, unlike sedatives, does not decrease voluntary or involuntary expulsive efforts. Averages for duration of the third stage are admittedly not important and are included only for the sake of completeness.

Cesarean section was performed in four of the total series of cases because of dystocia. While the findings in such abnormal cases markedly elevate the averages in the statistics for the entire series of cases, they have been included because each and every maternity case seen by us, while the investigation was in progress, received syntropan. In these cases the cervix dilated satisfactorily under the influence of syntropan, but the bony pelvis either did not permit delivery or a malposition existed, hence version, cesarean section, or forceps were employed.

The use of syntropan in labor apparently has no deleterious effect upon the infant. In the series of 102 cases (Table III), the condition of the infant immediately after delivery was "good" in 97 cases, "fair"



knowledge of the factors influencing sterility will expand in the future as rapidly as it has in the past few years.

In the present study it is proposed to report on some of the etiologic factors found in a group of 483 patients who sought admittance to the Gynecological Clinic of Bellevue Hospital, solely because of their inability to have a child or an additional child.

When the clinic was assured that the patient desired a baby and not simply an improvement in her own health, which some fancied a pregnancy would bring, a detailed history was taken upon a special blank designed to record pertinent factors in the past life of both husband and wife. The woman was warned that the investigations might take months and that treatment might require even a longer period of time. The patient was informed that she must be prepared to come to the clinic at weekly intervals or as often as advised.

A complete and adequate pelvic examination, including measurement of the uterus, was then performed and recorded. The woman was instructed to return with a specimen of her husband's semen the following week.

A complete routine study was then initiated on those women whose mates seemed to offer reasonable hope of fertilization. This study included a medical history, a complete physical examination in selected cases, a Rubin test with hysterosalpingography in doubtful cases, basal metabolism test, Wassermann test and an urinalysis. Cases of obvious endocrine dysfunction were referred to our Endocrine Clinic for study. Endometrial biopsy, cervical smear for gonococcus, complete blood counts, blood chemistry, reference to the medical clinic for systemic investigation were ordered as indicated. The weight, the date and duration of her last menstrual period were recorded upon each clinic visit. Many of the patients failed to return for complete investigation and our follow-up upon these cases was necessarily sketchy due to the floating character of the clinic population and our lack of a special worker to trace them. Therefore, some of our records are incomplete both diagnostically and with respect to end results. Despite these drawbacks, however, we feel justified in reporting the incidence of etiologic factors so far as found.

Our patients were all married women of the lower economic and social strata. Their ages varied between 17 and 44 years. There were 26 under the age of 20 and 6 patients were over 40 years of age. Over half (276) were between the ages of 20 and 29. Two patients who had been married only two months, and in whom conception had not occurred, had become impatient and sought aid. These patients were examined and instructed to return later if conception failed to occur. Seven had been married fifteen years or more without a pregnancy. The longest duration of marriage was twenty-four years although this couple had had two children and two spontaneous abortions, the latest having taken place five and one-half years before admittance. Nearly half (239) were admitted to the Clinic following one to four years of married life. Eighty-three per cent (401) were admitted during the first nine years of marriage. There were 34 couples who had been married more than ten years with sterile unions and who still hoped

Dr. Morton, our associate, is investigating syntropan for its effect upon uterine motility. The question may be raised: if syntropan relaxes the cervix, what happens to the uterus? There is a report in the literature that this preparation may arrest threatened abortion. If such is the case, what would cause the drug to act at one time in pregnancy upon the corpus uteri and another time upon the cervix uteri? Surely there is need for adequate pharmacologic and physiologic study before free and indiscriminate clinical use is justified.

If labor is shortened, it may result either from increasing uterine contractions or by lessening resistance to dilatation and expulsion. It may take a very large series to establish statistically that the labor is shortened, and a larger number still to show that a shortened labor is possible without increased risk to either the mother or baby.

## SOME ETIOLOGIC FACTORS IN STERILITY\*

### A STUDY OF 483 PATIENTS ADMITTED TO THE STERILITY CLINIC, BELLEVUE HOSPITAL

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IT IS not our intention in the present study to review the literature nor outline the therapy of sterility. There have been greater advances in the diagnosis and treatment of sterility since 1920 than in the previous centuries. Because of this fact those with involuntary sterility have taken heart. Childless couples now seek medical counsel with far more justifiable optimism than ever before. In the past, manual examination with surgical correction of existent anatomic abnormalities, if found, were the sole procedures the physician had to offer. The results of this operative era were notoriously poor. Prior to 1920, the wife was considered the principal cause of sterile unions except wherein the husband was grossly and obviously incapable of performing the sex act. It remained for a widely dispersed group of pioneer workers, Huhner, Rubin, Ogino, Knaus, Hartman and many others, to alter our concept of sterility. Indeed, the whole field of normal human reproduction has been profoundly changed and clarified by the work of these men. There is room for additional clarification. For example, we have as yet no laboratory method of proving the fertility of a given semen specimen. Although we believe that for all practical purposes, we can recognize a really fertile specimen, an occasional exception is reported. However, an absence of spermatozoa or the finding of very few or only dead sperm in properly collected and transported specimens on repeated occasions is presumptive evidence of male infertility. It is now universally recognized that no sterile woman should be subjected to serious operation until her husband's semen is known at least to contain living spermatozoa. Even this commonsense dictum has been in force for an incredibly short time. It is to be hoped that our

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The frequency of coitus among 402 couples (83 per cent) was from one to four times a week. Among 46 couples who reported sexual intercourse more than four times a week, only 7 males had motile sperm. Of the 21 couples whose reported coital frequency was less than once a week only 6 had motile sperm.

The greatest frequency of coitus was 4 or 5 times daily, reported by a female dwarf (height 4 feet, 6 inches, weight 150 pounds). This woman had been married to her present husband four years and to a previous husband five years. Her tubes were patent. The uterus was fibrotic and retroverted. The lowest coital frequency reported was once in every two or three months. This woman had also been married previously. The reproductive organs were hypoplastic and she had twice conceived and aborted spontaneously. Her present husband's semen was found to contain actively motile sperm. Following treatment and coital instruction she conceived and gave birth to a normal child.

One hundred and fifty-five women attempted to evaluate their sexual desire; 108 (69 per cent) considered themselves normal in that respect, 41 (27 per cent) claimed to be frigid, and 6 (4 per cent) thought their libido greater than average.

Seventy-eight per cent of these wives stated that no measures had ever been employed to prevent conception since their marriage. Twenty per cent said they had practiced contraception (douche, condom, or withdrawal) early in their married lives but had discontinued it when they desired a child. Two women had relied upon a "gold ring" pessary inserted in the uterus. They reported 5 and 2 spontaneous abortions, respectively.

On admittance to the clinic, 25 per cent of the patients were found to be overweight, 24 per cent underweight, and 51 per cent within normal limits for their ages and heights. There was no significant difference between primary and secondary sterility groups in this respect.

The principal pathologic conditions discovered at the time of the preliminary pelvic examination are listed according to frequency of occurrence in Table II.

TABLE II. ASSOCIATED PELVIC PATHOLOGY IN 483 CASES OF STERILITY

	TOTAL	%	PRIMARY STERILITY	%	SEC- ONDARY STERILITY	%
No pathology	32	7.0	11	4.0	21	10.5
Adnexal pathology	280	58.0	167	59.0	113	57.0
Endocervicitis	230	48.0	139	49.0	91	46.0
Erosion	149	30.0	76	27.0	73	37.0
Retroversion	148	30.0	91	32.0	57	28.0
Infantilism	126	26.0	95	33.0	31	15.0
Fibroid uterus	52	11.0	34	12.0	18	9.0
Stenosis of cervix	16	3.0	11	4.0	5	2.0
Bicornuate uterus	3	0.6	3	1.0	--	--
Cervical polyp	3	0.6	2	0.7	1	0.5

It is rather surprising to review the relative incidence of the various types of pathology and to note how, with two notable exceptions, it varies little with the history of previous conceptions. Cervical erosion

to have children. Primary sterility was diagnosed in 284 cases. One hundred and ninety-nine patients with secondary sterility gave a collective history of 384 pregnancies, 225 of which had terminated in abortions and 159 in viable births. Among the 199 cases of secondary sterility, 42 (21 per cent) had been previously married, while among the 284 patients who had never conceived only 15 (5 per cent) were now married for the second time. Of the 199 patients who had previously been pregnant, 135 (68 per cent) had experienced one or more abortions. Of this group, 13 could be termed habitual aborters, having had from 3 to 8 spontaneous abortions each.

In 43 cases (22 per cent), sterility was preceded by 1 to 4 induced abortions. Four patients each gave a history of one ectopic pregnancy. One of the latter conceived while under treatment, but nidation was again extrauterine and a laparotomy had to be performed.

Those contributing etiologic factors reported in the medical histories, which were thought possibly pertinent to the present sterility were listed in Table I.

TABLE I. CONTRIBUTING ETIOLOGIC FACTORS TO STERILITY  
(REPORTED IN HISTORY)

	TOTAL	%	PRIMARY STERILITY	%	SEC- ONDARY STERILITY	%
Appendectomy	87	18.0	49	14.0	38	19.0
Mumps	51	11.0	32	11.0	19	10.0
Laparotomy (other than appendix)	47	10.0	20	7.0	27	14.0
Dilatation and curettage	26	5.0	8	3.0	18	9.0
Salpingitis	22	5.0	13	5.0	9	4.0
Leucorrhea	22	5.0	17	6.0	5	2.5
Sepsis (post-partum or postabortum)	15	3.0	--	--	15	8.0
Gonorrhea	14	3.0	9	3.0	5	2.0
Syphilis	8	2.0	4	1.4	4	2.0
Thyroidectomy	4	1.0	2	0.7	2	1.0
Difficult labor	2	0.5	--	--	2	1.0

There was little difference in the histories of the primary and secondary sterility except in those conditions which were directly dependent upon pregnancy and its termination. Laparotomy for appendicitis and other causes was found more frequently in the secondary sterility group while gonorrhea and its complications (salpingitis, hydrosalpinx, and leucorrhea) evidence a small but constant lead in the primary sterility group.

Our information concerning the male partner in these sterile marriages was sparse. The wives showed amazing ignorance of their husbands' pasts, and we had no facilities for interviewing the men themselves. The semen examination was our sole basis of evaluating the male fertility.

Some of those sterile males who appeared totally incompetent (azoospermia) were referred to urologists, chiefly Dr. Robert Hotchkiss, and some to Dr. Ira Kaplan for x-ray stimulation. Six husbands were known to have had gonorrhea, 1 syphilis, and 1 diabetes.

never conceived there were exactly 50 per cent on the plus side and 50 per cent on the minus side, while among those who had previously reported pregnancies, 61 per cent were above the zero point and 39 per cent were below it.

In 156 cases (32 per cent), sterility was considered absolute, due to the presence of azoospermia or closed tubes or both. This figure is in exact accord with that found by Meaker and Vose.<sup>3</sup>

The female partner was found to bear the responsible sterility factor in 253 (52 per cent) of our cases; the male alone in only 10 cases (2 per cent). Both partners were considered infertile in 206 (43 per cent) records. It is highly probable that the relative number of cases of divided responsibility would have been greatly increased if we could have examined the semen of all the male partners, since in nearly one-half of those wherein the wife was considered as infertile, the reproductive status of the husband was unknown. In 3 per cent of the total group no explanation for the failure to conceive was found. Indeed 6 individuals of this small subseries of 14 became pregnant while undergoing investigation.

In the entire series of 483 patients, 74 women (15 per cent) conceived to our knowledge. As already pointed out our follow-up was inadequate. Rarely do the clinic patients who achieve successful treatment feel called upon to report spontaneously their success. Inasmuch as the majority of the known conceptions were traced only through chance follow-up, we feel justified in our belief that other conceptions probably occurred which were not called to our attention. Nevertheless, the known cases of successfully treated sterility may be classified as follows: pregnancy occurred in 43 women (21 per cent) of those 209 individuals in whom the treatment of their sterility was considered to be potentially successful. This group included women with known tubal patency but whose mates disclosed apparent semen defects (short of azoospermia). In the 274 women in whom the prognosis for relief of their sterility was deemed to be poor, it was evinced that 21 individuals (11 per cent) subsequently were impregnated.

In but one case of the group of 43, in whom the prognosis for cure of sterility was considered hopeless, was the outcome of treatment successful. Two major factors militated against hope of pregnancy in this case, a negative Rubin test and a husband who exhibited inactive sperm. In this case the use of iodized oil, for an uterogram, following a previous Rubin test, revealed a patent right oviduct. This patient subsequently delivered two living children.

Nine patients who presented nonpatent tubes upon their admittance but who were mated to males with actively motile sperm, eventually became pregnant; while 21 cases exhibiting patent tubes but whose husbands gave suggestions of infertility, conceived. The prognosis for satisfactory treatment of sterility was somewhat better in the secondary sterility group (19 per cent) than in those having primary sterility (13 per cent). This was anticipated, as a greater relative number of cases (62 per cent) having an unfavorable prognosis were in the latter group than in the former.

occurred with greater frequency in those who had previously undergone childbirth or abortion while hypoplastic genitals were more often seen in those who had never conceived; but, in the majority, the two groups showed strikingly little difference. The much greater incidence of all types of pelvic pathology in our series as compared to that in Kotz and Parker's<sup>1</sup> group of private patients may be possibly and partially explained by the variants of economic status and medical care in the two groups. The above investigators found an average of but 2.5 sterility factors per couple, while we report 3.3 sterility factors. Meaker and Vose,<sup>2</sup> in a thorough study, report 4.8 factors in sterile unions. When one considers the type of patient encountered at Bellevue, we are certain that if we had been able to include detailed etiologic studies of the husbands, the number of sterility factors per couple would have been much higher.

Semen specimens were examined in 364 cases. In 54 (15 per cent) no spermatozoa were found (azoospermia). Dead sperm only (necrospermia) appeared in 5 per cent of the cases. In an additional 29 per cent of this group the semen showed some type of abnormality which was serious enough to warrant the classification of "infertile," 85 (23 per cent) specimens were considered to be "borderline" to "fair," while only 102 (28 per cent) samples appeared microscopically adequate so as to be pronounced definitely "fertile."

In many cases the patient left the clinic before the existing contraindications to a safe Rubin test could be eliminated. In some the pathology was too extensive ever to warrant insufflation.

The Rubin test was performed, however, one or more times in 275 cases. At the initial test, 158 (57 per cent) patients were found to have bilaterally patent tubes, 109 (39 per cent) patients with bilaterally nonpatent tubes, while in 8 (4 per cent) patients the tubes were reported as partially obstructed. Uterograms were made in 83 of the 275 cases. In 75 (93 per cent) cases the roentgenograms confirmed the Rubin test; in 8 (7 per cent) patients it was contradictory. In 4 of the latter group the Rubin test was subsequently proved correct (conception occurred).

Following repeated insufflation, 37 (34 per cent) of the 109 patients in whom the first test showed negative results, were found to have patent tubes and, of this group of 37 patients, 6 women (16 per cent) subsequently became pregnant.

The basal metabolism test, although considered highly desirable as a routine, was, due to limitations of facilities, actually performed in only 133 patients. Eighteen patients (16 per cent) were found to have basal metabolic rates below minus 10, while 23 patients (20 per cent) were found to have basal rates above plus 10. The basal metabolism rates of the primary and secondary sterility groups differed in that the latter presented a greater incidence of readings above plus 10 (31 per cent to but 13 per cent below minus 10). In primary sterility the incidence of elevated and subnormal basal readings differed much less, being 13 and 17 per cent, respectively. The difference in the two groups is more strikingly brought out by comparing the proportion of cases falling above and below the 0 point; among the patients who had

## NECROSIS OR THROMBOSIS IN THE ABNORMALLY BLEEDING ENDOMETRIUM?

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**L**OCALIZED areas of necrosis have not infrequently been described in hyperplastic endometriums. Although several textbooks of gynecologic pathology<sup>6c, 15, 11b</sup> refer to a necrotic process in the descriptions of abnormal endometriums, it is omitted in other well-known monographs.<sup>5, 7</sup>

In 1900 Cullen<sup>3</sup> demonstrated localized areas of necrosis in the hyperplastic endometrium. Fifteen years later, R. Schroeder,<sup>12</sup> in his classical paper on menstruation, emphasized the frequency of these patches in such endometriums and ascribed to the necrotic changes an important role in the vascular mechanism of abnormal bleeding. Subsequent investigators<sup>2, 3, 6a, 6b, 14, 16</sup> concurred with Schroeder on the frequency and probable significance of this observation. These lesions were found less frequently by Novak,<sup>11a</sup> who minimized their importance as a source of profuse bleeding, and regarded them as a result and not a cause of hemorrhage.

Robert Meyer<sup>10</sup> has been impressed with the frequent association of endometrial necrosis, stromal hemorrhage, and thrombosis of capillaries in cases of endometrial hyperplasia, but apparently reached no conclusion with regard to the necrosis.

In a series of cases of functional uterine bleeding, Fluhmann<sup>6a</sup> reported necrotic changes in 39 per cent of cases where the specimen was obtained while the patient was actually bleeding, and only in 0.05 per cent of nonbleeding cases. In a series of cases of endometrial hyperplasia,<sup>6b</sup> he encountered necrosis in 43 per cent of actively bleeding patients and only in 2 per cent of quiescent patients.

### MATERIAL FOR STUDY

All uteri and curettings received in the laboratory of the Beth Israel Hospital during 1940 and the first three months of 1941 were examined histologically (hematoxylin-eosin). Cases of pregnancy, malignant tumors, and infections were excluded from the study. There were 243 uteri and 136 curettings in this series.

From two uteri, representative blocks of tissue were cut in serial section and stained with hematoxylin-eosin and the Bielschowsky silver stain.

#### 1. HISTOLOGIC PICTURE OF ENDOMETRIAL "NECROSIS"

The "necrotic" patches are distributed irregularly in the upper layers and on the surface of the endometrium (Figs. 1 and 2), except when they occur in adeno-myotic structures. They appear as variously-sized and irregularly-shaped patches and stain a light pink to pinkish gray with hematoxylin-eosin. When such foci appear above a mucosal surface, whose continuity has been destroyed in the process of shedding, they are partly or completely encircled by a collar of stromal cells. Embedded within these homogeneous, hyaline-like plaques are leucocytes, free nuclei, and occasionally a few red blood cells (Figs. 2 and 3).

The endometrium, which harbors these changes, is striking, particularly the vascular components. Capillaries appear numerous, dilated, filled with red blood

Age of the women as an etiologic factor bore little significance in this series of sterility cases. Fifteen per cent of those patients under the age of 30 years and 12 per cent of those beyond that age ultimately conceived. Duration of marriage appeared to be a more significant factor: 18 per cent of women married less than five years became pregnant, while only 12 per cent of those married a longer time were rewarded by conceptions.

In the 74 patients who conceived, a total of 83 pregnancies occurred. Of these pregnancies, 19, more than one-fourth, terminated in spontaneous abortion, while a single gestation, being extrauterine, required salpingectomy.

Since the termination of this study an attempt has been made to follow our sterility patients through the early months of gestation. Corpus luteum hormone and vitamin E were administered to those who seemed inclined to abort. The data of this experience are not yet ready for publication.

#### SUMMARY

The records of 483 consecutive cases admitted to the Sterility Clinic of Bellevue Hospital have been analyzed for factors which were thought to have a probable bearing upon reproductive inadequacy.

An average of 3.3 "sterility factors" for each couple was found. This figure would undoubtedly have been higher if more extensive study of the male partners of our patients had been made.

The absolute and relative frequencies of the various factors found upon admittance are noted and discussed. The factors which seemed to be associated most positively with sterility in this series were adnexal pathology (both with and without obstruction of the Fallopian tubes), endocervicitis, seminal abnormalities, abnormalities of basal metabolic rate (deviations above and below the accepted norm), and duration of marriage.

The author wishes to express her appreciation to Dr. H. Harold Lardaro, Chief of the Sterility Clinic, for his cooperation, without which this study would not have been possible.

#### REFERENCES

- (1) Kotz, J., and Parker, E.: *AM. J. OBST. & GYNEC.* 37: 233, 1939. (2) Meaker, S. R., and Vose, S. N.: *J. A. M. A.* 115: 1426, 1940.

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McCorkle, H. J., and Bell, H. Glenn: *Hydrocele of the Femoral Hernial Sac*, *Ann. Surg.* 113: 264, 1941.

The authors stress the rarity of this condition and furnish the histories of three proved cases of their own. The factors involved in the formation of femoral hydrocele are mentioned. The presence of a potential or actual femoral hernial sac or an embryologic rest aids in the explanation of the presence of femoral hydrocele. The fluid can either come from the peritoneal cavity when there is a definite communication or by inflammation within the sac or by trauma. The latter are merely theoretical possibilities.

WILLIAM BERMAN



## 2. WHAT IS THE MECHANISM IN THE FORMATION OF THESE PLAQUES?

The sequence of events, as deduced from the study of the sections, appears as follows:

Dilated, blood-filled capillaries become thrombosed. The thrombi undergo hyalinization. As the surface of the endometrium is approached, the wall of the thrombosed capillary disappears, either partially or completely (Fig. 3). The end-



Fig. 3.—Thrombotic plaque; medium magnification. The original vessel wall cannot be recognized.

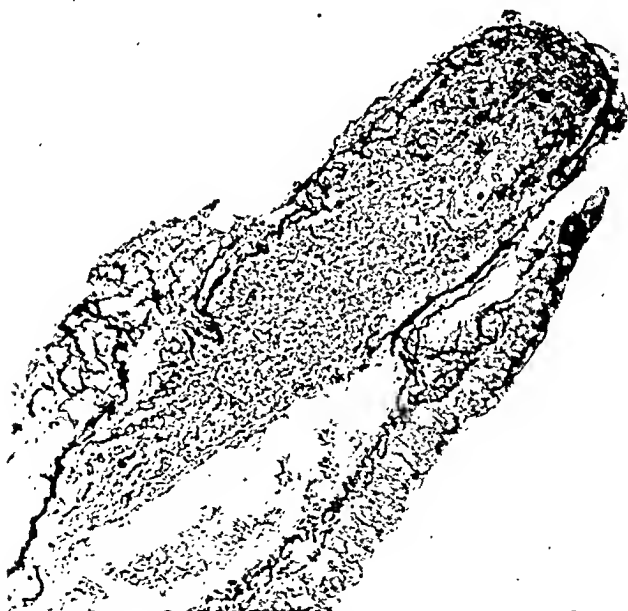


Fig. 4.—Thrombotic plaque. (Bielschowsky silver stain.) Remnants of the capillary wall can be seen.

cells, and are distributed throughout basalis and functionalis. Very often, capillary dilatation is extreme with formation of large venous sinuses, especially in the upper layers. Thrombosed capillaries and thrombosed venous sinuses make their appearance as the surface of the endometrium is approached. Invariably, such endometriums show leucocytes and hemorrhage in the stroma. The mucosal surface frequently has a ragged and moth-eaten appearance.



Fig. 1.—Thrombotic plaque in upper layer of endometrium. No vessel wall can be seen at the edge of the plaque. The intact surface epithelium runs across the left upper edge of the picture. The empty spaces surrounding the plaque probably are artifacts.

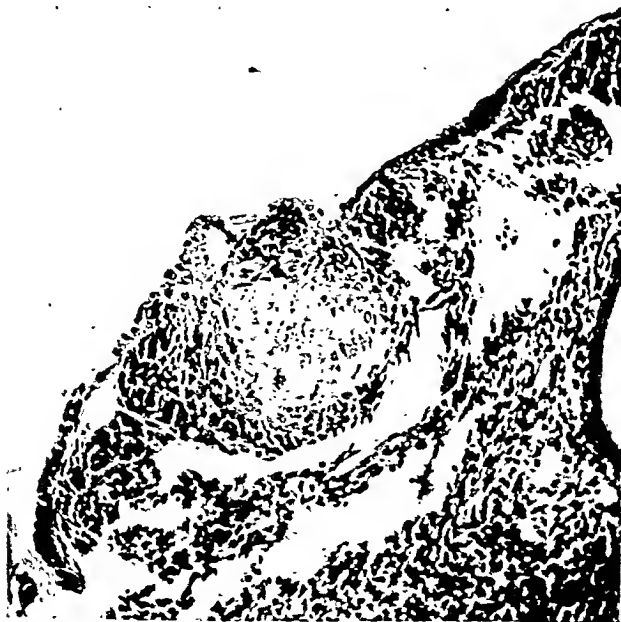


Fig. 2.—Small thrombotic plaque protruding from endometrial surface.

The frequent association of a thrombotic process in the endometrium with myoma and internal adenomyosis seems impressive. It appears less striking, however, when one considers that the indication for hysterectomy, in a majority of the cases, was a myomatous uterus, and that the uteri of the numerous curettings examined were usually normal or not sufficiently diseased to warrant removal.

Due to paucity of material, a study of associated ovarian disease was not attempted.

#### DISCUSSION

What have previously been regarded as localized areas of necrosis in the endometrium represent areas of capillary thrombosis, with partial or complete loss of the vessel walls, with progressive hyaline-like change of the thrombi, and a mechanical disintegration of the stroma. The breaking up of stromal and glandular components is not the result of a necrotic process, since no evidence of necrosis could be found. It may, in part, be attributed to the mechanical action of stromal hemorrhage, which is a concomitant feature of those cases. The elevation and detachment of masses of necrotic endometrial tissue by hemorrhage, followed by fissuring, as occurs during menstruation, was not observed in those endometriums in which thrombotic plaques were demonstrated.

Previous observers have called attention to the association of thrombosed capillaries and localized "necrosis" of the endometrium. R. Schroeder<sup>12</sup> postulated that these areas represent infarction due to thrombosis of vessels. Such a concept has been favored by others.<sup>2, 6a, 13, 16</sup> In this study we could not demonstrate the accepted criteria for infarction.

Apparently Teacher<sup>15</sup> did not regard these plaques as areas of necrosis. He studied them in serial sections and concluded that they were either thrombi, or the blob of a thrombus-like, slowly formed clot, which gathered around the end of a ruptured blood vessel and probably arrested the hemorrhage. Teacher has been impressed by the large, thin-walled vessels and general venous congestion of these endometriums, but was unable to express a definite opinion on the relation of this vascular picture to hemorrhage. He has described the surface stroma adjacent to the thrombotic plaques as "degenerative."

Necrosis does occur during menstruation.<sup>1, 9</sup> Thrombosis, which is so conspicuous a feature in the hyperplastic endometrium and other types of endometriums given to abnormal bleeding, apparently does not occur during menstruation. It was not observed in Markee's brilliant experiments<sup>9</sup> and was not alluded to in the exhaustive accounts on menstruation by Bartelmez.<sup>1a, 1b</sup> This suggests that the vascular mechanism of bleeding is altered in those endometriums which are the seat of thrombosis. The demonstration of thrombosis and of necrosis-like foci in endometrial hyperplasia induced in the castrated macaque by daily injections of estrone<sup>17</sup> supports such a thesis. The evidence that has accumulated in favor of the popular "withdrawal" theory in estrogenic bleeding<sup>8</sup> points in the same direction.

The most conspicuous feature of the endometrium, victim of thrombosis, as observed in this study, is capillary dilatation and capillary

result is a homogeneous, irregularly-shaped, light pink to pinkish gray patch, as described, or an area hardly absorbing any eosin. When patches, due to shedding, are situated above the mucosal surface, they are partly or completely enveloped by stromal cells, and even in this location an occasional strip of the previous capillary wall may be seen to hug some aspect of the margin of the patch (Fig. 4). The plaques which were studied in serial section revealed continuity with a blood vessel.

In no instance was any perivascular necrosis seen. At the surface of the endometrium, where the plaques are most usually encountered, there is a disintegration of the stromal and glandular components, a mechanical breaking-up of these tissues. Careful study of these bits of tissue always revealed intact cells. There was no histologic evidence of a necrobiotic process.

### 3. STUDY OF 243 UTERI AND 136 CURETTINGS

Thrombotic plaques\* were encountered in 62 cases (34 curettings and 28 uteri). They were seen approximately twice as often in curettings as in the extirpated uteri (Table I). In this group of 62 cases, the endometrium was hyperplastic in 34 (Table I), and a history of abnormal bleeding was obtained in 60 cases.

TABLE I. PHASE OF SPECIMENS CONTAINING THROMBOTIC PLAQUES

ENDOMETRIUM	UTERI, 28 CASES	CURETTINGS, 34 CASES
Proliferative	1	3
Secretory	1	2
Atrophic	5	9
Hyperplastic	19	15
Mixed	2	5

In the entire series of 406 specimens, there were 74 instances of endometrial hyperplasia. Of this group of 74 cases, thrombotic plaques were encountered in 34. In the remaining 40 cases of endometrial hyperplasia in which thrombotic plaques were not seen, 32 showed varying degrees of stasis, stromal hemorrhage, leucocytic infiltration, and 26 presented a history of abnormal uterine bleeding.

At no time were sections containing thrombotic plaques or thrombosed vessels seen in the absence of stromal hemorrhage.

Of this collection of 406 cases, we were able to obtain information as to whether the patient was actually bleeding at the time of operation in only 43 cases (mostly from the year 1941). The importance of such data has been emphasized by Fluhmann.<sup>6a, 6b</sup> In this group of 43 cases, thrombotic plaques were observed in 26, and of these, 22 occurred in hyperplastic endometriums (Table II).

TABLE II. CASES WITH UTERINE BLEEDING AT TIME OF OPERATION

	PROLIFERA-TIVE	SECRETORY	ATROPHIC	HYPER-PLASTIC	MIXED
Thrombotic plaques found	1	0	2	22	1
Thrombotic plaques not found	1	1	3	11	1

The uteri which contained thrombotic plaques were the seat of other lesions as follows:

Internal adenomyosis	8 cases
Myomas	15 cases
Hyperplasia of myometrium	2 cases
Myomas and internal adenomyosis	20 cases

\*The term, "thrombotic plaque," is employed in contradistinction to an easily recognizable, intraluminal thrombus.

field, Ill., 1939, C. C. Thomas. (9) *Markee, J. E.*: Contrib. Embryol. 27: 223, 1940. (10) *Meyer, Robert*: Henke-Lubarsch, Berlin, 1930, Vol. 7, Part 1, p. 128. (11) *Novak, E.*: (a) South. M. J. 25: 261, 1932; (b) Curtis' Obstetrics & Gynecology, Vol. 3, Philadelphia, 1933, W. B. Saunders Co., p. 124. (12) *Schroeder, R.*: Arch. f. Gynäk. 104: 27, 1915. (13) *Seitz, A.*: Ibid. 126: 252, 1922. (14) *Shaw, J.*: J. Obst. & Gynaec. Brit. Emp. 36: 1, 1929. (15) *Teacher, J. H.*: Manual Obstetrical and Gynecological Pathology, London, 1935, Oxford Medical Publications. (16) *Tietze*: Arch. f. Gynäk. 142: 680, 1930. (17) *Zuckerman, S.*: J. Obst. & Gynaec. Brit. Emp. 44: 494, 1937.

## HORMONE MANAGEMENT OF THE NAUSEA AND VOMITING OF EARLY PREGNANCY

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SO MANY of the pathologic conditions associated with pregnancy are evidences of hormonal dysfunction that we were tempted to apply the hormone key to the nausea and vomiting of early pregnancy, a condition that has long been regarded as a "toxemia."

Hawkinson<sup>1</sup> has already reported excellent results in these cases following the administration of estrogens, and Freeman, Melick and McClusky,<sup>2</sup> and Kotz and Kaufman<sup>3</sup> have published equally good results ascribed to adrenal cortex extract. Bandstrup<sup>4</sup> has been more cautious in recommending the latter, but admits that it undoubtedly cures certain patients with hyperemesis. Sussman<sup>5</sup> has advocated parathyroid extract together with calcium, and Falls<sup>6</sup> has used Lugol's iodine on the ground that many such patients display a transient hyperthyroidism.

### METHOD

I routinely do blood estrogen determinations<sup>7</sup> on antenatal patients as they present themselves. Clinically identical nausea and vomiting have been observed in both those with positive (high) and those with negative (normal or low) estrogen values, and therefore I have been disinclined to adopt the estrogen treatment of Hawkinson for all vomiting pregnant patients. It has seemed more logical to give estrogens to those with negative tests and an antiestrogen to those with positive tests. The antiestrogen selected has been testosterone propionate. It has proved much more efficacious than such antiestrogens as wheat germ oil or progesterone. Prolan preparations have not been tried. Where estrogens were used they were given in 10,000 international unit doses hypodermically every three days, if required by symptoms, and tablets were substituted as soon as feasible. When testosterone propionate was used it was given in 10 mg. doses similarly spaced, and in one of our recent successful cases the oral form was used.

### DATA

The cases were grouped approximately according to the plan used by Kotz and Kaufman, as follows:

Group A represents nausea and occasional vomiting.

Group B represents daily nausea and vomiting (occurring once or oftener each day).

stasis. Since vasoconstriction and vasodilatation play such vital roles in the normal bleeding mechanism,<sup>9</sup> some aberration of this rhythm probably occurs in those cases which exhibit thrombotic phenomena, particularly since the available evidence does not disclose thrombosis to be a feature of normal menstruation, and since the uteri, which contain thrombi, bleed abnormally. The thrombosis is, most likely, a result and not a cause of the profuse bleeding often seen in such cases, for thrombosis was never seen in the absence of hemorrhage, and yet hemorrhage was frequently observed in the absence of thrombosis.

Markee<sup>9</sup> has shown in the macaque that a few days prior to the onset of menstrual bleeding a phase of vasodilatation or stasis occurs. This is followed by vasoconstriction, which begins within twenty-four hours before the onset of bleeding. When a constricted artery relaxes, hemorrhage ensues. Bleeding ceases promptly when that artery is again constricted.

These observations, combined with our findings, might lead to the following theoretical considerations: The cycle is arrested during a phase of vasodilatation or stasis, or the vasodilatory phase of the regression stage is prolonged. This is followed by vasoconstriction of sufficient duration to produce damage to the capillary bed. With the release of the Daron<sup>4</sup> Type 1 arteries, bleeding begins. Tamponage effect (vasoconstriction) then takes place and bleeding ceases. Oozing continues from the engorged, injured capillary bed until the capillaries become thrombosed. An objection to such a hypothesis is that only about 25 per cent of the blood lost during menstruation is of venous origin.<sup>9</sup>

#### CONCLUSIONS

1. Areas previously regarded as necroses in hyperplastic endometriums represent thrombotic, hyalinized plaques, minus the vascular coat. They are embedded in a disintegrated but nonnecrotic stroma.

2. These foci are confined to endometriums which bleed abnormally, and are most frequent in the hyperplastic endometrium. They can be demonstrated if the specimen is obtained during, or immediately after, a bleeding episode.

3. Thrombotic phenomena are pathologic in the endometrium.

4. Correlation of this study with Markee's observations of the menstrual mechanism in the macaque is attempted and a hypothesis proposed.

I am deeply indebted to Dr. Alfred Plaut for his constant guidance and helpful criticisms.

#### REFERENCES

- (1) Bartelmez, G. W.: (a) *Contrib. Embryol.* 24: 141, 1933; (b) *Physiol. Rev.* 17: 28, 1937. (2) Burch, J. C., Phelps, D., and Wolfe, J. M.: *Arch. Path.* 17: 799, 1934. (3) Cullen, T. S.: *Cancer of Uterus*, New York, 1900, D. Appleton-Century Co. (4) Daron, G. H.: *Am. J. Anat.* 58: 349, 1936. (5) Deelman, H. T.: *Die Histopathologie der Uterusmucosa*, Leipzig, Georg Thieme, 1933. (6) Fluhmann, C. F.: (a) *J. A. M. A.* 93: 1136, 1929; (b) *Surg., Gynec. & Obst.* 52: 1051, 1931; (c) *Menstrual Disorders*, Philadelphia, W. B. Saunders Co., 1940. (7) Frank, R. T.: *Gynecological and Obstetrical Pathology*, D. Appleton-Century Co., 1931. (8) Hamblen, E. C.: *Endocrine Gynecology*, Spring-

## SUMMARY

1. Thirty-five patients with vomiting in early pregnancy were treated with testosterone propionate because they exhibited high blood estrogen levels; of these 80 per cent were cured and 14 per cent greatly helped.

2. Fifteen cases clinically identical, but with low or normal blood estrogen levels, were treated with estrogens; of these 73 per cent were cured and 20 per cent were much helped.

The author thanks Schering (Limited) of Canada for the supplies of progynon B, progynon DH, and oretone used in these clinical trials.

## REFERENCES

- (1) *Hawkinson, L. F.*: Minnesota Med. 19: 519, 1936. (2) *Freeman, W., Melick, J. M., and McClusky, D. K.*: AM. J. OBST. & GYNEC. 35: 618, 1937. (3) *Kotz, J., and Kaufman, M. S.*: Ibid. 39: 449, 1930. (4) *Bandstrup, E.*: J. Obst. & Gynaec. Brit. Emp. 46: 700, 1939. (5) *Sussman, W.*: AM. J. OBST. & GYNEC. 3: 761, 1937. (6) *Falls, F. H.*: See paper by Fitzgerald, J. E., and Webster, A.: Ibid. 36: 460, 1938. (7) *Shute, E. F.*: Ibid. 35: 970, 1938.

## A TWENTY-FOUR-HOUR PREGNANCY TEST

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FEW will disagree with Crew, of Edinburgh, when he states that, "among the instruments of precision that medicine has devised and used in the execution of its purposes and ideals, there is none finer than the biologic test for early pregnancy. Its value to the profession, to the general public and to the state . . ." is fully accepted.

A pregnancy test, to be of real value, must be correct in 98 to 99 per cent. Such accuracy had been attained in our laboratory when, in 1934,<sup>2</sup> we reported 1,093 Friedman tests of intrauterine pregnancy which showed false negatives in 0.55 per cent, and false positives in 0.09 per cent.\* To date the Friedman tests have reached 3,063 with 0.03 per cent false positives. In 1934 we pointed out that 3.4 per cent of rabbits proved refractory. The present data based on 3,063 tests show that of 2,116 rabbits used in "positive" urines, 134, or 6.3 per cent, proved refractory. This, therefore, further emphasizes our previous insistence that it is *essential to use two rabbits for each test*.

Numerous incorrect reports have come to our attention, emanating mainly from small neighborhood laboratories and from tests made by physicians who keep a few rabbits in their offices. Investigation has convinced us that the high cost of rabbits, the space required for housing them, the necessity of isolation for three to four weeks between tests if the animals are to be used repeatedly, in other words economic factors, account for the use of only one animal. In the hope of reducing the expense involved in performing a test for pregnancy, we have experi-

\*The results in extrauterine pregnancy, for reasons which we then discussed,<sup>2</sup> are of value only if positive.

Group C represents vomiting of all food.

Group D represents true hyperemesis, with the output greater than the intake.

GROUP	NUMBER OF CASES	BLOOD ESTROGEN VALUES	THERAPY	AVERAGE NUMBER OF TREATMENTS	RESULTS		
					CURE	HELP	NO HELP
A	13	8 (plus) 5 (minus)	Testosterone estrogen	4 hypodermics 2 hypos then tablets	5 3	2 2	1 0
B	25	17 (plus) 8 (minus)	Testosterone estrogen	5 hypodermics 2 hypos then tablets	13 6	3 1	1 1
C	8	8 (plus)	Testosterone	4 hypodermics	8	0	0
D	4	2 (plus) 2 (minus)	Testosterone estrogen	3 hypodermics 3 hypos then tablets	2 2	0 0	0 0
Total	50	35 (plus) 15 (minus)	As above	As above	39	8	3

### DISCUSSION

Widely varying types of treatment have been recommended in the literature for vomiting in early pregnancy and, surprisingly, each seems to help certain patients. Many of the women in our series had had prior trials of the usual sedatives, as well as frequent dry feedings, isolation and bed rest without any favorable effect being observed. On the other hand, three of the four patients in Class D and one in Class B did not react favorably to our treatment until they were hospitalized, when the identical therapy became effective immediately. One cannot completely discount the psychogenic factor in pregnancy vomiting, therefore. That the results achieved were not due entirely to psychic factors is demonstrated by the fact that sometimes an attempt was made to initiate hypodermic treatment, the drug used being based upon clinical judgment only, before the blood estrogen values had been reported. Where these clinical judgments proved to be incorrect in the light of the laboratory assay no help was obtained. When the assay report finally did come back and the more appropriate alternative substance was used hypodermically its beneficial influence became apparent at once, although the patient was not told that the treatment had been modified and of course had no way of knowing that such was the case. This fact seems to emphasize that there is no simple clinical method of accurately deciding to which type a patient belongs, for the symptoms are identical in high and low estrin types. It should also be noted that patients who resented hypodermic treatments highly insisted that they were much preferable to the vomiting they had experienced before such therapy had been instituted, and accordingly continued treatment until it became necessary no longer.

No explanation of the therapeutic effect obtained is attempted beyond the vague impression one gathers that the ship of pregnancy sails the estrogenic sea best at slack tide.



*Positive ovaries.*—The entire ovary presents a bright red haze. The majority of follicles are surrounded by a brilliant red zone and their surfaces covered by a minute capillary network, running toward the cap of the follicle. With the 10 diameter enlargement, the capillary network resolves clearly, the follicle then resembling the congested scleral conjunctiva of an inflamed eye (en miniature).

## ANATOMIC BASIS FOR THE TEST

Sections of positive twenty-four-hour ovaries show that the characteristic hyperemic zone is due to hyperplasia of the theca interna cells with marked multiplication and dilatation of the ingrowing capillaries.

Luteinization does not occur until forty-eight hours have elapsed, a fact of which we assured ourselves by performing 105 other tests and killing the animals after forty-eight hours. Fifty-six of these tests were positive and 49 negative, all agreeing with the clinical facts or parallel Friedman tests.

TABLE I  
NONPREGNANT

TYPE OF CASE	RAT TEST		RABBIT CONTROL	
	+	—	+	—
<i>Females</i>				
Miscellaneous	0	63	0	48
Ninth to fourteenth day of cycle	0	4	0	—
Amenorrhea	0	4	0	2
Menopause	0	6	0	3
Prepuberal	0	3	—	—
<i>Males</i>				
Miscellaneous	0	9	0	3
Eunuchoid	0	1	—	—
Prepuberal	0	2	—	—
Pemphigus	0	1	0	1
Pituitary tumor	0	2	—	—
Adrenal cortical carcinoma	0	2	0	1
Totals	0	97	0	58

## PREGNANT

DURATION OF PREGNANCY	RAT TEST		RABBIT CONTROL	
	+	—	+	—
Unknown	16	0	15	0
10 days	1	0	1	0
19 days	1	0	—	—
21 days	4	0	1	0
4-6 weeks	10	0	6	0
6-9 weeks	21	0	11	0
9-11 weeks	6	0	2	0
11-15 weeks	13	0	4	0
20-30 weeks	18	0	0	—
30-40 weeks	10	0	—	1(?)*
Totals	100		40	1(?)

Two cases could not be classified and must be regarded as doubtful because clinical outcome proved indecisive.

Case I: Overdue 2 days; urine gave positive rat test with 10 and 8 c.c.; no further urine available. She bled next day.

Case II: One episode of irregular bleeding, ectopic pregnancy suspected; 1 rat positive, 1 rat negative, 1 rabbit (no more urine available) negative; next day's urine negative in 2 rats and 2 rabbits.

Case III: Ectopic pregnancy, eighth week. Positive reaction. Findings confirmed by operation.

\*Patient in whom x-ray abortion was being induced. Gave positive rat, doubtful rabbit reaction.

mented since January, 1940, and have now evolved a technique which not only reduces the cost to one-quarter of the rabbit test but likewise shortens the time from forty-eight to twenty-four hours.

In addition to the Aschheim-Zondek test, which requires 5 mice and the elapse of ninety-six hours in time, and the Friedman test, requiring 2 rabbits and forty-eight hours in time, various other tests have been proposed. None of these, with one exception, approach the requisite accuracy. Among the proposed tests were the estrin, the fish tests, the allergic skin tests as well as the chemical tests, none of which have proved reliable.<sup>3</sup> The sole other test that appears dependable is based upon the injection of pregnancy urine into the lymph sac of the South African frog (*Xenopus laevis*)<sup>4</sup> which is followed in six to eight hours by the deposit of ova within the cloaca. This frog, however, is not available generally in this country.

The test which we present, in essence, is a modification of the Aschheim-Zondek test, two rats being employed instead of five mice, with reduction in time from ninety-six to twenty-four hours.

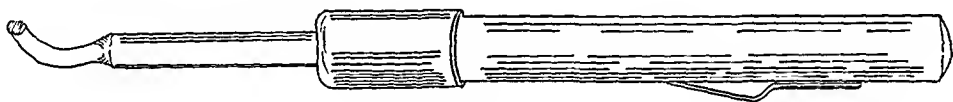


Fig. 1.

#### TECHNIQUE

*Animals Used.*—Two immature white female rats, each weighing 50 Gm., are employed. We use the Sherman strain albino but the Long-Evans strain has been found to react equally well.

Whenever possible, the first morning voided urine is used. Sediment is removed by centrifugation; urine is kept in refrigerator at 40° F. Before injection, allow urine to stand at room temperature for one-half hour to remove chill.

*Injection.*—Each rat received 10 c.c. of urine. Five cubic centimeters are injected subcutaneously under the loose skin of the back at 10 A.M. and the remaining 5 c.c. at 4 P.M.

The animals are killed the next morning (twenty to twenty-four hours after the first injection) with illuminating gas or chloroform. The abdomen is opened, and the ovaries removed with fine scissors and forceps, without traumatizing them. The ovarian bursa and tube are dissected away.

*Readings.*—Ovarian readings can be made by gross inspection.

*Negative ovaries* are small, pale, cream colored; the surface shows minute colorless follicles.

*Positive ovaries* usually are enlarged 3 to 4 times. Throughout, the ovary has a definite "blush." A few or many pinkish to red-capped follicles are noted.

*Lucite Readings.*—Further and more precise confirmation is obtained by examining the ovary by transmitted light with loupe magnification. The entire armamentarium consists of a small, curved, throat lucite rod, attached to a battery handle (see Fig. 1). The end of the lucite is filed off flat and then polished with fine emery paper. The ovary to be examined is lightly placed on the tip of the lucite rod without crushing its substance, and the light turned on. It is viewed through a 10 X Coddington Loupe.

*Negative ovaries* appear uniformly pale and cream colored. Not infrequently small red arteries are noted with no definite relation to the follicles. Here and there, between the follicles, a very faint pinkish tinge appears.

2. Two female white rats, weighing 50 Gm. each, are required for each test.

3. Five cubic centimeters of fresh urine are injected at 10 A.M. and 4 P.M. of the same day; the animals are autopsied at 9 A.M. of the next day.

4. The readings are made macroscopically and with 10 loupe enlargement by transmitted light.

#### REFERENCES

- (1) *Crew, F. A. E.*: AM. J. OBST. & GYNEC. 33: 989, 1937. (2) *Goldberger, M. A., Salmon, U. J., and Frank, R. T.*: J. A. M. A. 103: 1210, 1934. (3) *Weisman, A. I.*: AM. J. OBST. & GYNEC. 35: 354, 1938; *Kelso, R. E.*: Am. J. Clin. Path. 10: 293, 1940; *Falls, F. H., Freda, V. C., and Cohen, H. H.*: AM. J. OBST. & GYNEC. 41: 431, 1941. (4) *Bellerby, C. W.*: Nature 133: 494, 1934; *Shapiro, H. A., and Zwarenstein, H.*: Ibid. 133: 762, 1934. (5) *Frank, R. T., and Salmon, U. J.*: Proc. Soc. Exper. Biol. & Med. 32: 1237, 1935.

#### ADDENDUM

Since the acceptance of the manuscript, 32 additional twenty-four-hour pregnancy tests have been performed. Clinically all of these proved correct. Seventeen of the patients proved nonpregnant, 13 pregnant. The urines of two males, at first suspected of harboring chorionepithelioma of the chest, proved negative.

In the interim, efforts have been made to shorten the test still further. By trial it was found that a positive test could be obtained in eight hours, the 5 c.c. of urine being injected at two four-hourly intervals. Twenty-seven urines from pregnant patients gave 26 positive reactions. The sole negative was the urine of a patient, thirty-two weeks pregnant, who twice gave negative readings, with a week intervening between the tests, although the twenty-four-hour readings were positive. From this it would appear that when the indications are urgent, a positive test obtained after eight hours may be relied upon.

To date we have performed 201 tests by the twenty-four-hour technique described above. Of these, 97 gave negative, and 104 positive results. Detailed analysis of the findings is presented in Table I. In 98 cases, parallel Friedman tests were performed because the clinical course could not be followed. The rats used were given numbers and autopsy results recorded before the case histories were identified in order to eliminate prejudgment.

#### DISCUSSION

Analysis of our results has shown that the reliability of the test equals that of the original Aschheim-Zondek technique and is slightly more delicate than the Friedman test. Because of this, it was imperative to obtain a sufficient number of control cases in order to eliminate the possibility of false positives due to the presence of gonadotropic factors in the nonpregnant. The urine of normal women between the ninth and the fourteenth day of the cycle, at which time ovulation may be expected and which corresponds to the greatest accumulation of gonadotropic factors in the blood and urine,<sup>5</sup> gave a negative result. The urine of amenorrheic and menopause patients, in whom we had previously determined a high gonadotropic titer, likewise proved negative. Two urines from patients suffering with pituitary adenomas and two from patients with adrenocortical carcinoma, gave negative responses. The urines of children of both sexes before puberty likewise were negative.

A case of uterine chorioepithelioma gave positive results with as little as 0.05 c.c. of urine. In a normal pregnancy of eight weeks' duration, at which time the gonadotropic factors reach their peak, 0.1 c.c. of urine gave a positive reading; at twelve weeks positive tests were obtained with 0.2 c.c. Nevertheless 10 c.c. was selected for the test as even at that high level, 3.1 per cent of the rats proved refractory and no false positives were obtained in the absence of gestation.

The patients upon whom these tests were made, with the exception of a few private patients whose urines were sent in without data and on which a Friedman test was simultaneously performed as a control, have all been followed so that any discrepancy between the tests and the clinical course would become apparent. The few discrepancies are analyzed as footnotes to the chart.

As 10 c.c. of urine is a large dose for a 50 Gm. rat, it is necessary to obtain the urines fresh and to avoid chilling the animal, as previously mentioned. Stale urines prove lethal even when detoxified by ether extraction, as originally recommended by Zondek. Before this was noted, 8 per cent of the rats died, which, if anything, compares favorably with the more than 3,000 Friedman tests performed, in which 9.3 per cent of the rabbits were killed by the injection. Urines from patients receiving sulphanilamide or allied drugs proved lethal to the rats. We again repeat that it is *imperative to use 2 rats for every test* as at least 3.8 per cent have proved refractory.

#### SUMMARY

1. A simple, inexpensive pregnancy test requiring only twenty-four hours is described. Its accuracy is equal to the original Aschheim-Zondek and Friedman tests.

pipette. The vaseline is then permitted to harden. One test tube is placed in an incubator at 37° C. and the other test tube kept at room temperature (20° C.). Readings are taken every fifteen minutes.

The results of this experiment with 25 normal seminal specimens are charted in Table I. The semen had been collected in sterile wide-mouthed jars and was examined within one to three hours of the time of ejaculation.

Decolorization of the methylene blue was more rapid and completed earlier at 37° C. than at 20° C. At 37° C., decolorization began in fifteen minutes and was completed in one hour. Specimens kept at 20° C. began to decolorize in sixty minutes and were completely decolorized in one and one-half to two hours.

Two sets of control experiments were tried. One consisted of destroying the spermatozoa of 15 specimens by subjecting them to 65° C. for one hour before being tested by the above procedure. The other control consisted of removing the spermatozoa of 10 specimens by centrifuging at 3,000 revolutions per minute for one hour and testing the supernatant fluid according to the above procedure. All the control tubes were kept at 37° C. In every instance the methylene blue remained unchanged, showing that the spermatozoa were dead or absent (Table I).

TABLE I. RESULTS OF METHYLENE BLUE TEST FOR SPERM VIABILITY

DONOR	DECOLORIZATION TIME		CONTROLS INCUB. TEMP. 37½° C.
	INCUB. TEMP. 37½° C. MIN.	ROOM TEMP. 20° C. HR.	
1	50	1	No color change
2	40	1	No color change
3	30	1½	No color change
4	30	1¼	No color change
5	30	2	No color change
6	45	1	No color change
7	60	2	No color change
8	35	1¾	No color change
9	30	1	No color change
10	30	2	No color change
11	45	1½	No color change
12	60	1½	No color change
13	30	1¼	No color change
14	30	1	No color change
15	30	1½	No color change
16	40	1½	No color change
17	40	1½	No color change
18	30	1½	No color change
19	35	1¾	No color change
20	40	1½	No color change
21	60	1	No color change
22	35	1½	No color change
23	30	2	No color change
24	55	1	No color change
25	35	1½	No color change
Average	39	1 hr. 42 min.	

Another series of controls should also be made with seminal fluid presumed to be inadequate as to the number of spermatozoa and percentage of abnormal forms. Unfortunately these specimens were not available for study. It is likewise possible that the rate of conversion of the methylene blue to its colorless base may be significant of the degree of viability of the spermatozoa. These are problems worthy of further investigation.

#### SUMMARY

A simple and practical method of determining sperm viability is described, utilizing methylene blue as an indicator of the absorption of free oxygen by spermatozoa.

# STUDIES IN VIABILITY OF HUMAN SPERMATOZOA

## PRELIMINARY REPORT

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THE office determination of sperm viability is measured by their motility in a hanging drop preparation. Vigorous and progressive movement across the microscopic field is characteristic of healthy normal spermatozoa. Sluggish movements or absence of movement within one hour of the time of ejaculation is generally interpreted as a sign of lowered or absent spermatie vitality.

A better understanding of the conditions affecting sperm motility indicates that the problem of sperm vitality is not so easily solved. Factors such as viscosity, osmotic pressure, pH, temperature, oxygen concentration, all affect the metabolism of the living spermatozoa and may individually or in combination affect their motility.<sup>1-7</sup> Moench,<sup>1</sup> for example, ingeniously proved that sperms stored in the epididymis remain practically motionless due to lack of oxygen and a strongly alkaline medium, yet they are very much alive as evidenced by their activity in the ejaculate.

It would seem advisable therefore, when spermatozoa exhibit deficient or absent motility, to obtain additional information in regard to their vitality.

The procedure to be described is based on the property of living spermatozoa, like all living cells, to utilize available free oxygen. Methylene blue is used as an indicator because of its ready conversion to colorless leucomethylene blue when deprived of oxygen, and because it is non-toxic. Thus, when methylene blue is added to spermatie fluid in an anaerobic preparation, the available oxygen is utilized by the living spermatozoa. The loss of this oxygen from the preparation causes the methylene blue to change to its colorless state. On the other hand, if the spermatozoa are dead, the dye maintains its blue color because there is enough free oxygen present to prevent any change to the leuco base.

## METHOD

The procedure adopted consists of placing 1 c.c. of spermatie fluid and  $\frac{1}{10}$  c.c. of methylene blue solution\* in each of two ordinary Wassermann tubes. The test tubes are inverted several times to insure thorough mixing, care being taken to avoid air bubbles. A little heated vaseline is layered over the mixture by means of a

\*The methylene blue is prepared as follows:

Sodium chloride	9.2 Gm.
Sodium bicarbonate	0.05 Gm.
Potassium chloride	0.1 Gm.
Calcium chloride	0.1 Gm.
Distilled water	1,000 c.c.

Dissolve the above and adjust the pH to 7.8-7.9. Then add 0.2 Gm. of methylene blue. Shake until the dye is dissolved, filter and use.

countries but only a very few in the United States. It is to be noted that the procedure is frequently referred to as the Portes-Gottschalk operation. Gottschalk of Germany described a similar technique to that of Portes as far back as 1909, but to the best of our knowledge never performed such an operation.

Phaneuf<sup>3, 4</sup> believes that the Portes operation is reserved for the occasional hopelessly infected patient wherein the matter of the time element is a serious consideration. This author had performed two of these procedures up to 1937, resulting in two maternal recoveries and the survival of one infant. The uterus was exteriorized for forty-one days in the case of the first patient and for thirty days in the second.

The operation itself, as described by Portes, is done in two stages. The initial portion of the procedure includes an abdominal incision, the delivery of the pregnant uterus, the closure of the abdominal wall behind the uterus down to the cervix, a high uterine incision, extraction of fetus, membranes and placenta, closure of the uterine defect allowing the uterus to remain on the abdomen, and wet packs to the wound.

The second stage follows only after the complete healing of the uterine incision and consists of re-opening the abdominal incision, freeing whatever adhesions which may have formed, dropping the uterus and adnexa back into the pelvic cavity, draining the area posterior to the uterus and closing the abdomen. Several of the French authors, however, have deemed it necessary to remove the uterus following its exteriorization owing to excessive and prolonged infection.

The mortality rate from this seemingly extensive procedure is not high considering that most cases so treated were definitely infected. Couvelaire,<sup>5</sup> in 1925, reported a mortality of 6.2 per cent in 32 cases. We know of Phaneuf's good results in two cases.

In 1938, Parsons<sup>6</sup> reported three neglected cases seen in China and treated by this method. None of the babies was living on admission to the hospital. One mother recovered and 2 died of heart failure after operation. All 3 cases showed evidence of frank infection.

#### DISCUSSION

Of the comparatively few authors who have written on this subject all seem to agree that the Portes operation is primarily of value in markedly infected cases wherein a Porro type of section would consume too much time. Therefore, the most important indications for the procedure seem to be neglected individuals in whom a frank infection is present and who manifestly are poor surgical risks. All authors claim a very short operative time for the Portes section, twenty-five to thirty minutes appearing to be about the average duration for completion of the first stage operation. It is, however, our impression that the procedure can be done little, if any, faster than the Porro section. We realize that practice aids in a swifter technique but the first stage operation in the case to follow required only thirty minutes. The Porro operation, in most competent hands, takes little longer and seems to us the safer procedure in the majority of cases although it must be admitted that the amputation of the uterus plus the uterine incision in this operation allows for the possible spill of infectious material into the peritoneal cavity. The case herein reported represents a 23-year-old primigravida who was just beginning her reproductive life. In this particular subject it would have been regrettable to have removed her uterus at the time of abdominal section. Therefore, since the time element is practically of no import in evaluating the Porro and Portes

The authors wish to express their thanks to Dr. Harry Aranow, Director of Obstetrics at Morrisania City Hospital, and to Drs. M. J. Goodfriend and A. B. Tamis who helped in organizing the material for this paper.

## REFERENCES

- (1) *Moench, G. L.*: AM. J. OBST. & GYN. 38: 153, 1939. (2) *Killian, J.*: Am. J. Surg. 19: 76, 1933. (3) *Baker, J. R.*: J. Hyg. 31: 189, 1932. (4) *Cody, B. A.*: J. Urol. 13: 175, 1925. (5) *Muschat, M.*: Surg., Gynec. & Obst. 42: 778, 1926. (6) *Cohn, E. J.*: Biol. Bull. 34: 167, 1918. (7) *Jahnel, F.*: Klin. Wchnschr. 17: 1273, 1938.

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## THE PORTES CESAREAN SECTION WITH REPORT OF A CASE\*

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THE choice of treatment in definitely infected labor cases has been a moot question for many years. Classical cesarean section may be mentioned only to be condemned when performed upon a frankly infected case. The low cervical section with transverse cervical incision is perhaps somewhat more adaptable. Latzko introduced an extra-peritoneal section, hoping it would prove to be the logical procedure in such cases. This operation, however, has great technical difficulties. Within the past year Waters<sup>1</sup> and Smith<sup>2</sup> each have suggested modifications of the Latzko procedure. Such operations, if technically not too difficult, would probably offer the greatest degree of success in the treatment of neglected individuals. These authors admit that the procedures are time consuming. In the poor surgical risk a shorter operation is advisable. The Portes type of section answers this need. It has the disadvantage of including two separate stages and a prolonged hospitalization for the patient. It has the distinct advantage of precluding the spill of infectious material into the abdominal cavity since the peritoneum is closed before the uterus is entered. This, of course, does not hold true in the Porro section wherein the uterus is removed supravaginally after the infant is extracted. Because of the more or less general debate and argument as to the proper method of handling patients exhibiting evidence of infection, it seemed worthwhile to present a brief résumé of appropriate literature on the subject together with a case report. The Portes section performed upon this woman was the first ever done in the St. Louis University Group of Hospitals.

### REVIEW OF LITERATURE

In 1923 at the Maternité de Port Royal de Paris, Dr. Louis Portes first performed a cesarean section followed by temporary exteriorization of the uterus. Since that time, a number of these operations have been done in France and other foreign

\*Presented before a combined meeting of the Kansas City, Chicago and St. Louis Gynecological Societies, St. Louis, Mo., February 15, 1941.



## MENORRHAGIA AS A PRIMARY FACTOR IN VARIOUS BLOOD DYSCRASIAS

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**G**YNECOLOGIC symptoms of systemic disease are by no means uncommon. Menstrual disturbances, such as amenorrhea and menorrhagia, are quite characteristic of generalized cachexia due to any cause. Occasionally, however, the gynecologist is confronted with a presenting symptom so characteristically gynecologic in type that the actual etiologic factor is discovered only after extensive systemic investigation, or by the sudden exacerbation of generalized symptoms of a disease which had previously manifested itself in abnormal menstrual function only. Frank<sup>1</sup> has recently stated, "It is now accepted that functional diseases of the female may originate not only in the ovary, but also in the pituitary, adrenal, or thyroid glands." In addition to these endocrine factors he might have added abnormalities of the hematopoietic system, because the actual occurrence of uterine bleeding is affected by the condition of the blood vessels and the blood itself. Various blood dyscrasias, such as purpura hemorrhagica, aplastic anemia, or leucemia, ordinarily have easily identifiable diagnostic characteristics. Occasionally, however, their presenting and only symptom is menorrhagia, and it is with these latter cases that we are directly concerned.

This condition has received some attention in the literature in the form of isolated case reports, Israel and Mendell<sup>2</sup> having reviewed the subject in 1939 and added a case of their own. Jennings and Castle-den<sup>3</sup> reported another case from England in the same year, but, so far as we know, there has been no attempt made to evaluate the frequency with which gynecologic abnormalities are the presenting symptoms of these disorders.

A brief review of 108 cases of purpura hemorrhagica, aplastic anemia, and leucemia taken from the record files of the Presbyterian Hospital reveals that no less than 10 of these patients presented themselves for medical treatment with a chief complaint of menorrhagia. In many other cases this gynecologic symptom occurred as one of the incidental factors in a condition already diagnosed, yet in this series an incidence of nearly 10 per cent of cases of blood dyscrasias were first seen in a gynecologic clinic or were first treated for their gynecologic complaint.

Various treatments for uterine bleeding were instituted before other systemic manifestations of the actual hematopoietic pathology presented themselves. Local treatment was carried out in 3 cases, vaginal packing being used in 1, curettage in another, and hysterectomy in a third subject. Four patients received various types of medication,

techniques, we believe the general indication for the Portes type of section should include frankly infected cases in which the mother is early in her reproductive life.

In 1937, M. P. Huet<sup>7</sup> pointed out, in referring to the original work of Louis Portes, that the first operation of this kind was done on an infected individual, aged 21 years. Portes conceived his idea of exteriorizing the uterus because he believed that section followed by hysterectomy would have been a regrettable choice in so young a woman.

#### CASE REPORT

The patient, seen in Firmin Desloge Hospital on May 29, 1940, was a 23-year-old primipara whose pregnancy, until the time of labor, presented nothing unusual. Her pelvic measurements were apparently normal. The blood pressure had been moderately elevated and for this condition she had had some treatment. When first seen her temperature was 102° F. and pulse 120. The white blood cell count was 20,000 with a shift to the left in the differential. The membranes had ruptured forty-eight hours previously, and she had been in fairly strong labor for three days. The abdominal examination revealed a uterine pregnancy of approximately full term with a right position. The fetal heart tones were good in the right lower quadrant. The rectal examination revealed the presenting part, the head, high in the pelvis. It was ascertained by questioning that both the patient and her husband were desirous of future pregnancies and because of this fact and the evidence of frank infection in so young a woman, a Portes type of cesarean section was decided upon. The patient was given several vaginal instillations of an antiseptic solution and taken to the operating room where the abdomen was opened under gas anesthesia. The uterus was delivered through the incision and the peritoneum was then closed about the uterus. An incision was then made into the uterus and a full-term male infant, weighing 9 pounds 3 ounces was delivered from an R.O.P. position. The cry and respiration were spontaneous. The placenta was removed manually and a foul odor arising from the uterine cavity was noted. The uterine incision was then closed, leaving the uterus outside the abdominal cavity. The time consumed in this procedure was thirty minutes.

Following this operation the patient ran a temperature of 101 to 103° F. for several weeks. Neoprontosil was given in large amounts together with several blood transfusions. The area around the uterine wound sloughed extensively despite the presence of constantly wet saline packs. This condition finally was controlled sufficiently to permit the second stage operation fifty-five days after the original procedure.

On the twenty-fourth of July, 1940, the patient was again anesthetized, the uterus was freed from its attachments to the abdominal wall and the abdominal cavity was re-opened. The uterine fistula was closed with 2 rows of catgut sutures. The raw uterine surface was covered with bladder peritoneum and the uterus was dropped back into the pelvic cavity. The right tube was found to be patent but a probe could not be passed into the left tube. The abdomen was closed in layers. This procedure, which was made exceedingly difficult due to a retraction of the peritoneum, was completed in slightly less than two hours and was complicated only by the development of a small abdominal wall fistula which was treated by styptics and which gradually healed. The patient left the hospital on Sept. 4, 1940, exactly ninety-eight days after the initial operation. She has menstruated regularly since then and to all external evidence is in good condition.

#### REFERENCES

- (1) *Waters, E. G.*: AM. J. OBST. & GYNEC. 39: 423, 1940.
- (2) *Smith, E. F.*: Ibid. 39: 763, 1940.
- (3) *Phaneuf, Louis*: Am. J. Surg. 35: 446, 1937.
- (4) *Idem*: Surg., Gynec. & Obst. 44: 738, 1927.
- (5) *Couvelaire, A.*: Bull. Soc. d'obst. et de gynec. de Paris 14: 148, 1925.
- (6) *Parsons, E.*: AM. J. OBST. & GYNEC. 35: 311, 1938.
- (7) *Huet, M. P.*: Mem. Acad. de Chir. 63: 40, 1937.

including vitamin C, chorionic gonadotropic hormone, snake venom, and ergot. Transfusions were administered to 2 of these patients. A brief outline of the history and treatment is tabulated in Table I.

#### CASE REPORTS

54403.—The patient was a 28-year-old female with a complaint of menorrhagia for two years with profuse uterine bleeding for three weeks. About one year after onset of menorrhagia she developed pallor, weakness, and ecchymoses. She had previously received chorionic gonadotropin therapy. A diagnosis of aplastic anemia was made, and the patient subsequently died.

444336.—A 54-year-old woman complained of profuse menorrhagia for which hysterectomy was performed. No pathology was observed in the uterus following removal. Weakness, loss of weight, and anemia became progressive following operation. A diagnosis of aplastic anemia was made. Patient died two years postoperatively.

377204.—A 15-year-old girl complained of menorrhagia which was thought to be functional in origin. Subsequent blood counts disclosed the presence of purpura hemorrhagica. Splenectomy was performed with subsequent cessation of menorrhagia.

581584.—Patient was a 21-year-old girl with chief complaint of menorrhagia. Subsequent history disclosed the presence of occasional epistaxes and ecchymotic spots. Purpura hemorrhagica was diagnosed on the basis of blood counts. Splenectomy resulted in cure.

563291.—A 20-year-old girl complained of menorrhagia. Dilatation and curettage was performed without relief, and three months later epistaxis and bleeding from gums occurred. Purpura hemorrhagica was diagnosed on the basis of blood counts. Splenectomy resulted in cure.

551210.—Patient was a 27-year-old female with chief complaint of menorrhagia. She received snake venom and transfusions without relief. Four months after onset of menorrhagia, ecchymoses appeared. Blood counts disclosed presence of purpura hemorrhagica. Splenectomy resulted in cure.

463987.—A 42-year-old woman complained of menorrhagia. She received ergot without relief and was admitted for operation. Routine blood counts disclosed presence of purpura hemorrhagica. She underwent a spontaneous remission and has been well since.

77477.—A 23-year-old girl whose chief complaint was profuse vaginal bleeding for seven weeks. Subsequent history disclosed presence of frequent ecchymoses. Purpura hemorrhagica was diagnosed on basis of blood counts. Splenectomy resulted in cure.

482332.—A 33-year-old woman had suffered a six months' miscarriage with profuse bleeding, and subsequent menometrorrhagia was unrelieved by packing. Two months later miscellaneous ecchymoses and epistaxis occurred. Diagnosis of purpura hemorrhagica was made on basis of blood counts. Splenectomy resulted in cure.

315921.—An 18-year-old girl complained of menorrhagia for which she received "pills and medicine." Two weeks later onset of menorrhagia, bleeding gums, and purpuric spots appeared. Diagnosis of acute lymphatic leukemia was made. Patient died.

TABLE I. CASES OF BLOOD DYSCRASIA IN WHICH MENORRHAGIA WAS THE INITIAL SYMPTOM

CHART	AGE	CHIEF COMPLAINT	PREVIOUS TREATMENT	OTHER SYMPTOMS	DATE OF APPEARANCE OF OTHER SYMPTOMS AFTER ONSET OF CHIEF COMPLAINT	DIAGNOSIS	RESULT
544403	28	Menorrhagia 2 yr. Profuse 3 weeks	Vitamin C Transfusion Antuifrin	Pallor Weakness Ecchymoses	About 1 yr.	Aplastic anemia	Died
444336	54	Vaginal hemorrhage 2 yr. ago	Hysterectomy	Anemia Weakness Loss of weight Fatigue	Since operation	Aplastic anemia	Died
377204	15	Menorrhagia (Functional?)			With chief complaint	Purpura hem-orrhagica	Splenectomy
581584	21	Menorrhagia		Ecchymoses Epistaxis	With chief complaint	Purpura hem-orrhagica	Splenectomy
563291	20	Menorrhagia	Dilatation and eu- retage	Epistaxis Bleeding from gums	3 months	Purpura hem-orrhagica	Splenectomy
551210	27	Menorrhagia	Transfusion Snake venom	Ecchymoses	4 months	Purpura hem-orrhagica	Splenectomy
463987	42	Menorrhagia	Ergot	None		Purpura hem-orrhagica	Spontaneous Remission
77477	23	Vaginal bleeding for 7 weeks		Ecchymoses	With chief complaint	Purpura hem-orrhagica	Splenectomy
482332	33	6 months' miscarriage with profuse bleeding. Menorrhagia since	Packing	Ecchymoses Epistaxis	2 months	Purpura hem-orrhagica	Splenectomy
315921	18	Menorrhagia	"Pills and medi- cine"	Purpuric spots Bleeding gums	2 weeks	Acute lym- phatic leu- cemia	Died

done on each ovary. Histologic study revealed a small dermoid cyst in the section removed from the right ovary and a follicle cyst of the left ovary. Careful study of the resected tube did not reveal any evidence of tuberculosis. On the eighth day postoperatively, the patient passed grossly bloody urine and had severe epistaxis. Except for slight secondary degree anemia, blood studies were normal.



Fig. 1.—Case M. K. Endometrium obtained by suction curettage, following 372,400 R.U. of  $\alpha$ -estradiol benzoate intramuscularly, 860,400 R.U. of  $\alpha$ -estradiol orally, and 20 mg. of progesterone. Note atrophy of stroma; few small scattered endometrial glands. ( $\times 50$ .)



Fig. 2, A.—Case M. K. Endometrium following 1,028,000 R.U. of  $\alpha$ -estradiol benzoate in oil, 860,400 R.U. of  $\alpha$ -estradiol orally, and 120 mg. of progesterone. Note marked necrosis. ( $\times 50$ .)

## SUMMARY

Ten cases of blood dyscrasias are presented whose presenting symptom was menorrhagia. Seven patients were variously treated for their gynecologic complaints before subsequent characteristics of the blood dyscrasia manifested themselves.

## CONCLUSION

Although the total number of cases of uterine bleeding having occult blood dyscrasias must be relatively small, it is considered significant enough to warrant complete blood studies on every unexplained case of menorrhagia.

## REFERENCES

- (1) *Frank, R. T.*: AM. J. OBST. & GYNEC. 40: 574, 1940. (2) *Israel, S. L., and Mendell, T. H.*: Ibid. 38: 339, 1939. (3) *Jennings, G. H., and Castleden, L. I. M.*: Lancet 1: 931, 1939.
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## AMENORRHEA DUE TO TUBERCULOUS ENDOMETRITIS

## FAILURE OF ESTROGENS AND PROGESTERONE TO INDUCE UTERINE BLEEDING

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IT IS generally accepted that functional amenorrhea is caused by a deranged activity of the endocrine glands. The fact that the end organ, viz., the uterus, may be at fault, failing to respond to what normally would be adequate hormone stimulation, has received but scant attention in the literature. The case reported here illustrates this point, that is, the finding of tuberculous endometritis in a patient with secondary amenorrhea in whom enormous doses of estrogen and progesterone failed to induce uterine bleeding.

## CASE REPORT

The patient was a 23-year-old, unmarried, nulligravida, admitted to the Ward Service on Oct. 18, 1934. Her chief complaint was amenorrhea. The past menstrual history was significant. Menses began at the age of 16 and occurred at regular twenty-eight-day intervals. The flow was scant and lasted only two days. In 1930, the menses became irregular and then stopped completely in February, 1931. In June, 1934, the patient menstruated spontaneously for four days. The past medical history was noncontributory. There was no history of contact with tuberculosis. General physical examination revealed normal findings. Pelvic examination showed an intact hymen, moist, adult type of mucosa and a uterus of normal size. The ovaries were enlarged to approximately two times the normal size. The basal metabolic rate was within normal limits.

The findings on exploratory laparotomy were a small uterus in midposition, and the right tube clubbed, slightly enlarged and adherent to a polycystic ovary 3 to 4 cm. in diameter. A moderate-sized hydrosalpinx was present on the left. The left ovary was also cystic and the same size as right. Small wedge resections were

The patient was again seen in the out-patient department in September, 1936, approximately two years following operation, complaining of vertigo, asthenia, and nervousness. There had been no uterine bleeding since operation and no flushes. However, it is noteworthy that, following operation, epistaxis had occurred at fairly regular monthly intervals. At this time, the patient was started on estrogen therapy and received continuous treatment from Dec. 6, 1937, to Aug. 15, 1938.  $\alpha$ -Estradiol benzoate was administered 2 or 3 times weekly, in individual doses, varying from 4,000 R.U. to 10,000 R.U., supplemented by oral therapy (18,000 R.U. of  $\alpha$ -estradiol, daily). The total dosage administered over this period of time was 372,400 R.U. of  $\alpha$ -estradiol benzoate, intramuscularly, in addition to 860,400 R.U., orally. Without interruption of the estrogen administration, the patient was then given 20 mg. of progesterone in 5 mg. doses, over a period of two weeks, and a suction curettage was done. Only small fragments of endometrium were obtained which showed atrophy of the stroma and a few scattered glands (Fig. 1). Because of the slight evidence of estrogenic stimulation of the endometrium, we concluded that the patient had received an inadequate amount of estrogens. The dosage of estrogens was, therefore, increased to 10,000 R.U. of  $\alpha$ -estradiol benzoate, 3 times weekly.

From Aug. 15, 1938, to Feb. 27, 1939, a total dosage of 656,000 R.U. was administered. In addition, from Jan. 30, 1939, to Feb. 27, 1939, the patient received 100 mg. of progesterone, in 10 mg. doses. In spite of the enormous doses of estrogens and progesterone, bleeding did not occur, and an endometrial biopsy by suction curettage was done.

Dr. Paul Klemperer, pathologist at the Mount Sinai Hospital, New York, described the specimen obtained as follows: "Section shows several particles of necrotic tissue (Fig. 2, A) in which only sporadic fragments of endometrial glands can be recognized. Some of the fragments show, in addition, slight infiltration with polynuclear leucocytes. There are other particles which show granulation tissue, including several large tubercles with caseous centers surrounded by a wreath of epithelioid cells (Fig. 2, B) and also tubercles including giant cells of the Langhans type (Fig. 2, C). The histologic picture is unmistakably that of tuberculosis, but tissue stains for tubercle bacilli were negative. (From the academic point of view, it would have been desirable to obtain fresh endometrial tissue for injection into guinea pigs in order to demonstrate tubercle bacilli. However, this was not done because of the danger of reactivating the disease.) The presence of caseation and typical tubercles is regarded as sufficient proof of the diagnosis. Furthermore, the fact cannot be denied that a severe necrotizing process has destroyed most of the endometrium."

A complete physical examination and x-ray of the chest failed to reveal any evidence of tuberculosis. The patient at the present writing has been observed for more than one year since the last endometrial biopsy. There has been no uterine bleeding and the pelvic examination remains unchanged with no clinical evidence of tuberculosis.

#### DISCUSSION

It is an open question whether the amenorrhea in this case was caused by the cystic disease of the ovaries, the tuberculous endometritis, or by a combination of both. The failure of the endometrium, however, to respond to the huge doses of estrogens and progesterone suggests either impairment of the normal proliferative property inherent in the endometrium and/or actual destruction of the endometrial glands and stroma, both of which are probably attributable to the tuberculous process. It has been our experience that the atrophic endometrium, even as long as thirty years after the cessation of ovarian function (spontaneous or castration), can be stimulated to a degree of proliferation and differentiation comparable to that which prevails in women with normally functioning ovaries. The dosage used in the case reported here was far in excess of the amount required to produce such a physio-

Hemoglobin was 87 per cent; red blood cells, 3,710,000; white blood count, 8,300; platelets, 230,000; polymorphonuclears: 68 per cent nonsegmented, 1 per cent segmented, 2 per cent eosinophiles, 18 per cent lymphocytes, 9 per cent monocytes; bleeding time, one and one-half minutes; coagulation time, 11 minutes; and tourniquet test, negative. The postoperative course, thereafter, was uneventful.



Fig. 2, B.—Case M. K. Another area of same biopsy showing tubercle formation with central caseation and epithelioid cells. ( $\times 50$ .)



Fig. 2, C.—Case M. K. High power magnification of Fig. 2, B, revealing tubercle formation and Langhans type giant cells. ( $\times 275$ .)



partum hemorrhage ensued which was said to be due to the rupture of a small artery beneath the urethra. On the eighteenth post-partum day, while at home, another severe hemorrhage occurred which was controlled presumably by packing the vagina. On her first visit, four years after delivery, she complained of brownish discharge from the vagina, of one week's duration, coming on two days after the expected menstrual period was due. The patient was frightened because she thought she was suffering from ectopic pregnancy since two of her friends had recently died of that condition. Pelvic examination showed slight enlargement of the uterus and no adnexal disease. The cervix appeared normal with the exception of a small polypoid nodule about one-fourth inch in diameter, which was attached to the portio vaginalis on the right side. It was suggestive of malignancy. No discharge from the cervical canal was noted, but a slight brown discharge from the growth was observed. The growth was removed and the pathologist reported it to be composed of decidual glands and cells. The diagnosis, obviously, was an endometrial transplant which had undergone decidual formation. The patient returned in two weeks as the bleeding had continued. Pelvic examination at the time revealed the cervical growth to be two or three times its original size, and it continued to have a brownish discharge. The uterus was the size of a two and one-half to three months' pregnancy with slight enlargement in the right cornual region. A few days later an operation was done, because of the marked and unexplained change in the uterus. The endometrial implant was excised and a curettage was done. Normal tissue of an early pregnancy was removed. A laparotomy was then done and the only essential finding was a bicornuate uterus with enlargement of the right portion.

By way of explanation for this unusual occurrence Rushmore logically deduced that some endometrial tissue became lodged in a laceration of the cervix at the time of the first delivery, became embedded there and started growing.

#### CASE REPORT

G. C., a white woman, aged 40 years, a private patient of Dr. H. S. Crossen, was admitted to Barnes Hospital with the complaints of irregular vaginal bleeding, pain in the lower abdomen, and backache. In her past history the only relevant information was that in 1932, she had a uterine suspension, left salpingo-oophorectomy, right salpingectomy, and appendectomy. Menstruation began at 13 years of age and was regular every twenty-eight days until 1930. At that time the interval shortened to every twenty-three days and the flow lasted for seven days. Following the operation in 1932, her periods again became regular every twenty-eight days until the present illness which began two years ago. The only significant fact in her marital history was that she had two pregnancies twelve and fourteen years ago which terminated in full-term, normal deliveries. Her present illness started two years ago with metrorrhagia. For the past two months the bleeding had been continuous.

Physical examination was essentially negative except for the pelvic findings. Pelvic examination revealed a chronic cystic cervicitis, with an irregular and enlarged corpus the size of a fist. The adnexa were not palpated (removed at previous operation).

*Findings at the Operation.*—The abdomen was opened through a median sub-umbilical incision. Extensive adhesions were present along the old incision. Adhesions to the abdominal wall were separated only sufficiently to obtain adequate exposure of the pelvic structures. The corpus uteri was enlarged two and one-half times and densely adherent to the left side of the pelvis. The omentum, sigmoid and bladder were incorporated in the mass. It required very careful dissection to separate the sigmoid from the uterus, in fact, it was necessary to excise some of the uterine tissue in order to avoid injury to the gut. The adherent bladder was separated from the front of the uterus. By careful dissection, the bladder, then the uterus were freed from the mass. The uterus was found to be regular but enlarged. A complete hysterectomy was done. The pedicles were ligated and the vaginal vault closed about a red rubber tube drain, Dakin size. There was no evidence of pelvic endometriosis.

logical endometrial pattern. In view of these observations, we would advise that an endometrial biopsy be performed in all cases of functional amenorrhea prior to the institution of hormone therapy and that the presence of some destructive disease of the endometrium should be suspected if bleeding fails to occur after adequate therapy.

#### SUMMARY

A report has been presented of a case of secondary amenorrhea, treated with 1,028,000 R.U. of  $\alpha$ -estradiol benzoate in oil intramuscularly, 860,400 R.U. of  $\alpha$ -estradiol orally, and 120 mg. of progesterone, over a period of approximately fourteen months, without causing uterine bleeding. Suction curettage, following the hormone therapy, revealed atrophy of the endometrium and tuberculous endometritis. Attention is drawn to the possibility of disease of the endometrium, such as tuberculosis, causing amenorrhea by impairing the normal proliferative capacity of the endometrium or by actual destruction of the endometrial tissue. The suggestion is made that an endometrial biopsy be done in all cases of functional amenorrhea before institution of treatment and repeated if bleeding does not occur after adequate hormone therapy.

For the  $\alpha$ -estradiol (progynon-DH) and the  $\alpha$ -estradiol benzoate (progynon-B) used in this investigation, we are indebted to Dr. Erwin Schwenk and Dr. Max Gilbert, of the Schering Corporation, Bloomfield, N. J.

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#### PRIMARY ENDOMETRIOSIS OF THE CERVIX UTERI

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PRIMARY intracervical endometriosis is very rare. A survey of the literature reveals only one case in which there has been direct extension of the endometrium or transplantation on the mucosal side of the cervix. The other cases that have been reported and those that we have observed have been extensions from a rectovaginal septum involvement or transplants on the posterior surface of the supravaginal portion of the cervix. We do not consider as endometriosis (endocerviosis), cases in which cervical glands penetrate deep into the fibromuscular stroma. Teacher and others have reported such cases. There is a marked variation in the normal depth of penetration of cervical glands into the fibromuscular stroma. It is obvious that erosions and lacerations with ectropion change the distribution of the endocervical tissue so that great difficulty may arise in determining whether or not it is abnormally situated or a result of invasion. At any rate the appellation is a misnomer, for the tissue does not simulate endometrium in any respect.

Rushmore, in 1931, reported an unusual case of primary endometriosis of the cervix and stated that a careful search of the literature failed to show a similar case. His patient was a young, white woman, who had been delivered by version and extraction by another physician four years previously. An immediate post-

myometrium was diffusely infiltrated with round cells and the blood vessels showed changes characteristic of mild subinvolution. The sections through the portion of the cervix described as having a papillary character and brownish discoloration showed normal, stratified, squamous epithelium with many cervical glands, several of which were dilated into cystic structures (Nabothian cysts). One small area showed typical endometrial glands embedded in characteristic stroma (Figs. 1 and 2). Other sections were then taken from this area, and the same histopathologic picture was present. Many sections were taken from the posterior portion of the cervix and the uterus, and no evidence of endometrial tissue could be observed.

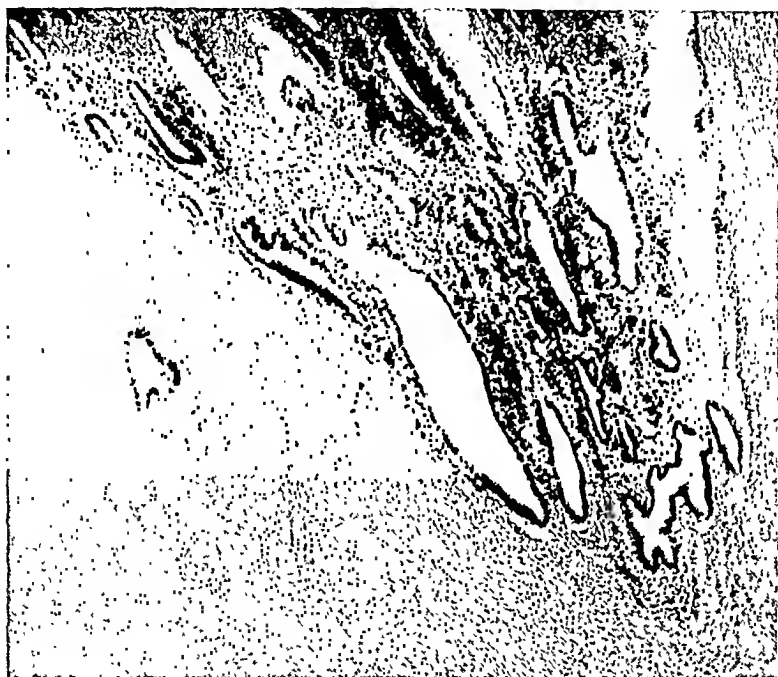


Fig. 2.—Higher power photomicrograph of area labelled C in Fig. 1, showing the character of the endometrium.

#### DISCUSSION

To us this is unequivocally a case of primary endometriosis of the cervix. We feel that the most likely explanation is that endometrial tissue became entrapped in a cervical laceration, but the possibility that it became implanted on a diseased or intact mucous membrane cannot be dismissed.

Our familiarity with the wide dissemination of endometrial tissue and the relative ease of transplantation, inadvertently at operation or experimentally, has often stimulated us to speculate on the apparent infrequent occurrence of endometriosis of the cervix, per se. The cervix is ideally situated for transplantation to occur. At each menstrual cycle, fragments of endometrium pass over the intact cervical mucosa which is apparently resistant to the growth of this tissue itself and perhaps serves as a barrier against invasion into the fibromuscular stroma. On the other hand the cervical mucosa is frequently lacerated by abortion, full-term labor, dilatation, curettage, and many other operative procedures. During a curettage, the cervical mucosa is often scraped away

The appendix, left ovary, and both tubes had been removed at a previous operation. The right ovary was somewhat cystic and contained a corpus luteum. Since the patient was only 40 years of age, the operator considered it best to empty the cyst and preserve the ovary. The abdominal incision was closed without drainage. The patient was in good condition throughout the operation. Spinal anesthesia, supplemented by gas and ether toward the end, was used. An indwelling catheter was placed in the urinary bladder.

*Pathologic Examination.*—Gross examination revealed a complete uterus measuring in the fixed and open state 8 by 5 by 4 cm. The cervix measured 4 cm. in diameter and 4.5 cm. from external to internal os. The portio vaginalis was covered by normal epithelium and the surface was smooth and glistening. The



Fig. 1.—A low power photomicrograph of section taken at external os, showing squamous epithelium A covering the cervix; B, cervical glands, and C, an island of endometrial tissue.

cervical canal appeared normal with the exception of a small area, 0.5 cm. in diameter, located near the external os on the right side, which was brownish in color and papillary in character. There were several adhesions over the posterior surface of the corpus. The myometrium measured  $2\frac{1}{2}$  cm. in thickness and showed gross evidence of subinvolution. The endometrium measured 3 mm. in thickness and was rather velvety. Several blocks were taken through the cervix and the uterine wall for microscopic study.

Microscopic examination of the sections taken through the uterine wall showed normal interval type endometrium with a diffuse round cell infiltration. The

## LEIOMYOSARCOMA OF THE UTERUS ASSOCIATED WITH RAMIFYING ANGIOMYOMA

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VASCULAR neoplasms of the uterus remain unusual and interesting tumors. There are at present 39 recorded cases<sup>1</sup> of benign hemangiomas, the majority of which have been associated with leiomyofibromata. This case is reported as an instance of a peculiar vascular process associated with a leiomyosarcoma of the uterus.

Mrs. C. R. (248,281), a 39-year-old white married housewife, was admitted to the Jersey City Medical Center on Oct. 20, 1939, complaining of profuse menstrual bleeding of nine months' duration.

Nine months before admission her menstrual flow became profuse and many clots were passed. This continued for sixteen days and was accompanied by severe cramps. Menorrhagia of a similar nature has persisted, although one or two periods were of three days' duration with but a moderate flow and less severe cramps. Four months before admission appeared a dull dragging lower abdominal pain which has been progressive. During the past three months mild headaches have accompanied her menses. Two months before admission the patient noted nocturia, two to three times, as well as infrequent dribbling with coughing or sneezing. The patient had previously been in good general health with the exception of the usual childhood diseases, and a tonsillectomy had been performed when she was 14 years of age. Five years ago she experienced an attack of epigastric pain of several days' duration, and since that time she has noted intolerance to fried or fatty foods. Her menarche occurred at 10 years of age; her periods occurred regularly each twenty-eight days, lasted three to four days, and were accompanied by moderately severe cramps. She has two healthy children and two abortions occurred at two months' and three months' gestation, respectively.

Physical examination revealed a well-developed and somewhat obese, middle-aged white female who did not appear acutely ill. The temperature was 98.6° F., the pulse 78, respiration 22, and blood pressure 112/80. The general physical examination was essentially normal. The abdomen was obese and lower abdominal striae were present. There was slight tenderness in the left lower quadrant without rebound tenderness or rigidity. A firm irregular, 5 cm. mass was felt directly above the symphysis. Pelvic examination disclosed cervical erosions and lacerations. The uterus was grapefruit in size and the ovaries were not felt.

The urinary findings were within normal limits. The hemoglobin was 70 per cent, the red blood cells numbered 3.4 million, and the white blood cells 9,200, with 63 per cent polymorphonuclear leucocytes.

Laparotomy was performed on the following day. The uterus was enlarged to three times its usual size, and irregular in contour. A 4 cm. irregular, moderately firm mass extended from the left fundal wall into the broad ligament. A total hysterectomy and bilateral salpingo-oophorectomy were performed.

The patient made an uneventful postoperative recovery and was discharged on the fifteenth hospital day. At the present time, eighteen months after her admission, large firm pelvic masses can be felt by bimanual examination.

The surgical specimen consisted of a complete uterus, two tubes, and two ovaries. The uterus measured 15 by 6 by 5 cm. Its smooth surface was interrupted by a 0.5 cm. firm pedunculated subserous mass. A somewhat softer, roughly round, lobulated, smooth, 4 cm., light pink mass was broadly attached to the left side between the peritoneal folds of the broad ligament, and smaller portions of similar tissue surrounded the lower portion of the uterus. The myometrium was 2.5 cm.

to determine if a polyp or malignant growth may exist in the cervix, the fibromuscular stroma is wounded, and freshly removed, viable endometrial tissue becomes smeared over the injured surface. The fact that the lesion is so infrequent in the cervix, notwithstanding ample opportunity for implantation, justifies the obvious conclusion that the cervix is hostile to the growth of endometrial tissue. It is well known that tubal mucosa, germinal epithelium, and peritoneal mesothelium may undergo further differentiation into tissue which morphologically and functionally is identical with endometrium. These tissues have a common ancestor, the mesenchyme, and therefore, have the potentiality of developing into like tissue. The cervical mucosa is Müllerian in origin and, therefore, shares this common ancestor with the above-mentioned tissues so that the latent potentiality for differentiation into endometrial tissue exists. Three questions arise: first, does cervical mucosa ever undergo mutation into endometrial tissue? It is theoretically possible, but to our knowledge there is no evidence to support such an assumption. Second, what factor or factors inhibit this permutation in the cervix? We refrain from attempting to answer the latter question, because it would be purely speculative in nature. Third, why is the cervix so infrequently involved in primary endometriosis? We suggest a change in pH may be a factor in inhibiting the growth of endometrial tissue in the cervix. Those opposed to this theory may point out that implants occasionally occur in the vagina and perineum where there is normally a considerable change in the hydrogen ion concentration toward the acid side. Again theorizing, it may be possible that these implants occur only in the cervix, vagina, and perineum where there is an abnormally high pH due to some intravaginal disease.

#### SUMMARY

Endometriosis of the cervix is rare. Most of the cases that do occur are secondary to endometrial transplants in the rectovaginal septum, or are implants on the posterior surface of the supravaginal portion of the cervix. This is the second case reported of a primary endometrial transplant. Since the cervix is ideally situated for implantation to occur, the obvious conclusion is that the cervix for some unexplained reason is inimical to the growth of endometrial tissue.

#### REFERENCES

- (1) *Cullen, T. S.*: Adenomyoma of the Uterus, Philadelphia and London, 1935, W. B. Saunders Co., p. 165.
- (2) *Idem*: Arch. Surg. 1: 215, 1920.
- (3) *Landau, L., and Pick, L.*: Arch. f. Gynäk. 64: 98, 1901.
- (4) *Rushmore, S.*: New England J. Med. 205: 149, 1931.
- (5) *Sampson, J. A.*: Arch. Surg. 3: 245, 1921.
- (6) *Teicher, J. H.*: Manual of Obstetrical and Gynecological Pathology, London, 1935, Oxford University Press, p. 229.

fairly well-circumscribed, submucous mass which was partially covered with intact endometrium and had a whorled, yellowish white cut surface with small, irregular, dark red areas of hemorrhage. The endometrium was smooth and yellowish white with a blood-tinged surface. The cut surfaces of the parauterine mass were homogeneous and light pink with small areas of hemorrhage.

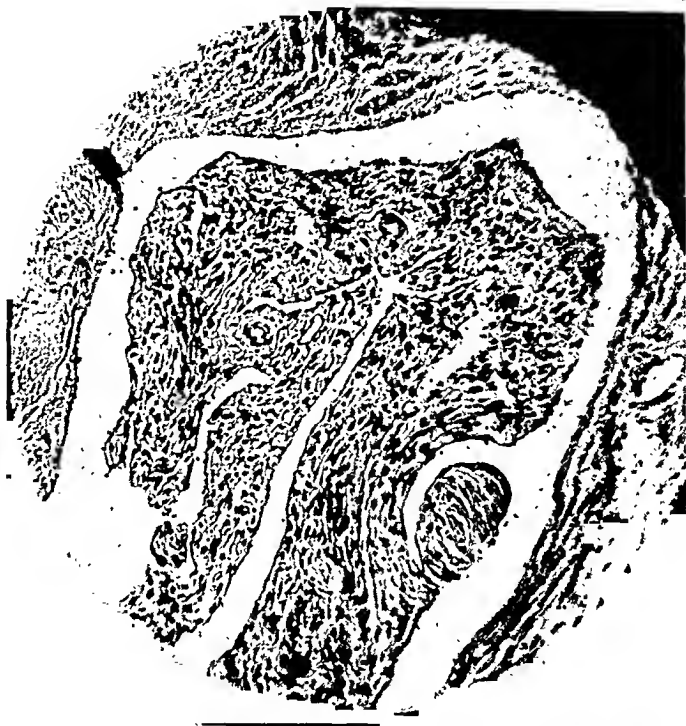


Fig. 3.—An intravascular process of elongated hyperchromatic cells supporting dilated capillaries and small arterioles.

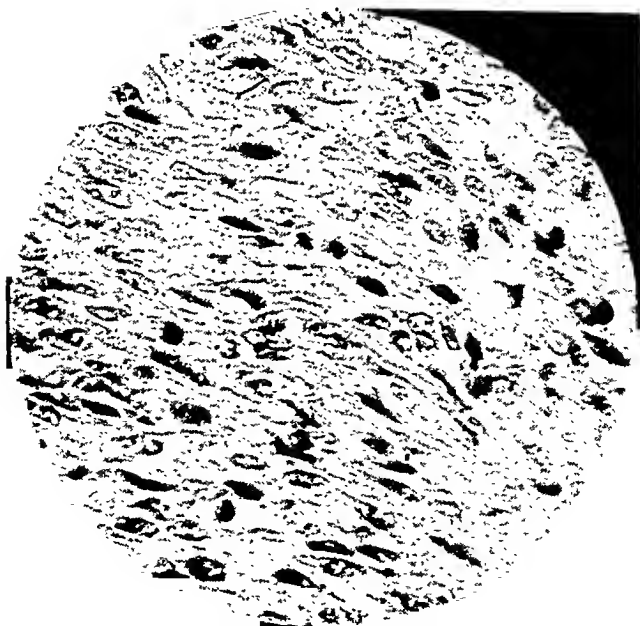


Fig. 4.—Elongated cells with hyperchromatic nuclei and mitotic figures.

in thickness, firm and light pink. Near the periphery were several quite well-circumscribed soft, spongy, honeycombed, 0.5 to 1.5 cm., pink areas. Within the midportion was a 0.3 cm., well-circumscribed, firm, translucent, white area with a whorllike appearance. The endometrial cavity was compressed by a 3 cm. round,



Fig. 1.—Dilated tortuous endothelial-lined tubes and a cellular stroma supporting well-developed arterioles and capillaries.



Fig. 2.—Thrombosis within one of the large vascular channels.



One ovary measured 2.5 by 2 by 1 cm. On section, it presented several 0.5 cm., smooth lined cysts containing clear straw-colored fluid and a 0.5 cm. yellowish lined body filled with clotted blood supported by firm, white, ovarian stroma. The other ovary measured 3.5 by 2.5 by 2 cm. and contained similar cysts.

Microscopically, the myometrium is interrupted by several circumscribed areas composed of numerous dilated vascular channels lined by small endothelial cells (Fig. 1). Many of these spaces contain thrombi (Fig. 2). The supporting stroma contains short spindle-shaped cells, numerous small capillaries, well-developed arterioles, and areas of well-differentiated smooth muscle. Within larger channels are intravascular projections of elongated spindle-shaped cells (Fig. 3). The margin of the tumor is quite well demarcated from the myometrium. The single submucous mass is composed of closely related spindle-shaped cells with hyperchromatic nuclei which are occasionally seen in mitosis (Fig. 4) and numerous large bizarre multinucleated giant cells (Fig. 5). Sections of the parauterine mass reveal chaotically arranged, moderately acidophilic, short spindle-shaped cells with oval or elongated nuclei rich in chromatin and with a moderate number of mitotic figures. Small capillary vessels are numerous (Fig. 6). There is hyperplasia of the endometrium, the ovaries contain hemorrhagic follicular and lutein cysts, and there is moderate fibrosis of the tubes.

#### COMMENT

Horgan<sup>2</sup> distinguishes true cavernous hemangiomas from hemangiomatous fibromyomas in which circumscribed areas of greatly enlarged vessels occur only within the smooth muscle tumor. Gardner<sup>3</sup> uses the term "fibromyoma angiomatosum" to indicate an abundance of normally developed arteries within cellular fibromyomas.

The present case has many features similar to the ramifying angiomyoma of the uterus published by Pusch<sup>4</sup> in 1932. He described a 0.1 to 1.5 cm., branching, truncated mass of soft pink tissue ramifying through the myometrium from cornu to cornu and readily separated from the myometrial bed. A small, soft, red, globular structure bulged from the cut surface of the left broad ligament. Histologically the tumor was composed of conspicuous blood vessels and smooth muscle fibers arranged in cordlike structures which frequently occupied dilated venous channels. There was no fusion of the neoplasm to the adjacent myometrium.

The angiomatous tissue in our case could not be directly traced to the sarcomatous nodule. We are prejudiced to the opinion that the vascular process is independent of the leiomyosarcoma.

#### REFERENCES

- (1) *Kevorkian, A. Y.*: New England J. Med. 223: 1, 1940. (2) *Horgan, E.*: Surg., Gynec. & Obst. 50: 990, 1930. (3) *Gardner, G. H.*: AM. J. OBST. & GYNEC. 40: 822, 1940. (4) *Pusch, L. C.*: Ibid. 24: 907, 1932.

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**Findley, G. M.**: Chemotherapeutic Investigations on the Virus of Lymphogranuloma Venereum, *Lancet* 2: 682, 1940.

Experiments on mice, infected intracerebrally with the virus of lymphogranuloma venereum and treated daily by mouth with 10 mg. per 20 Gm. mouse, showed that under the experimental conditions employed the most active compound was sulfamethylthiazole, followed by sulfapyridine, sulfathiazole, sulfanilamide, lutazeol and di-sodium 4:4'-bis-o-carboxylbenzoylamidodiphenylsulphone. Unfortunately in man sulfamethylthiazole may occasionally cause polyneuritis so that sulfapyridine remains the most effective drug clinically available. With sulfapyridine 50 of 100 inoculated animals survived in comparison to 13 survivals among 100 control inoculations.

CARL P. HUBER

Each tube measured 4.5 cm. in length and 0.8 cm. in diameter. The surfaces were smooth. On section, the musculares were well preserved, and the mucosae intact.

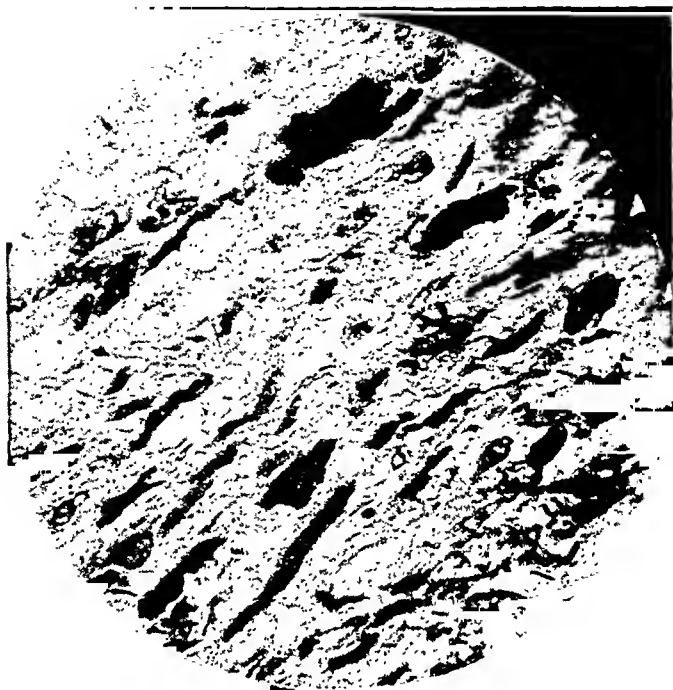


Fig. 5.—Bizarre multinucleated giant cells.

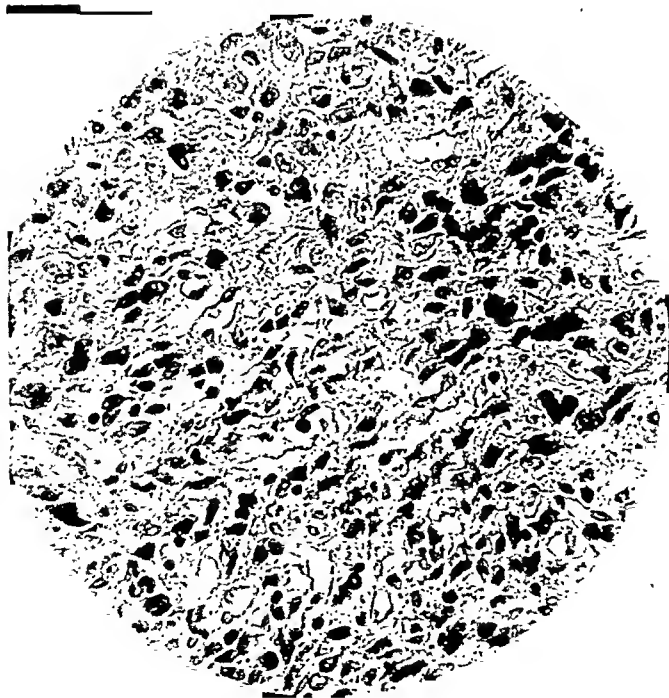
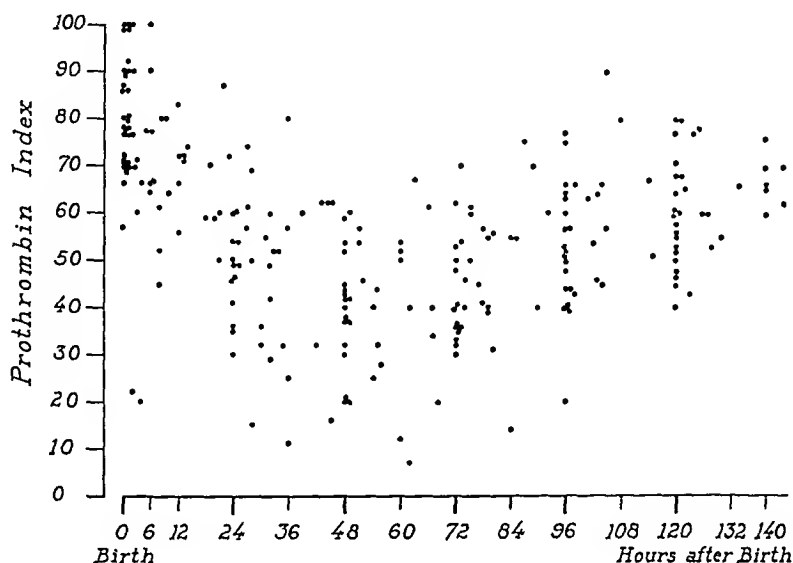


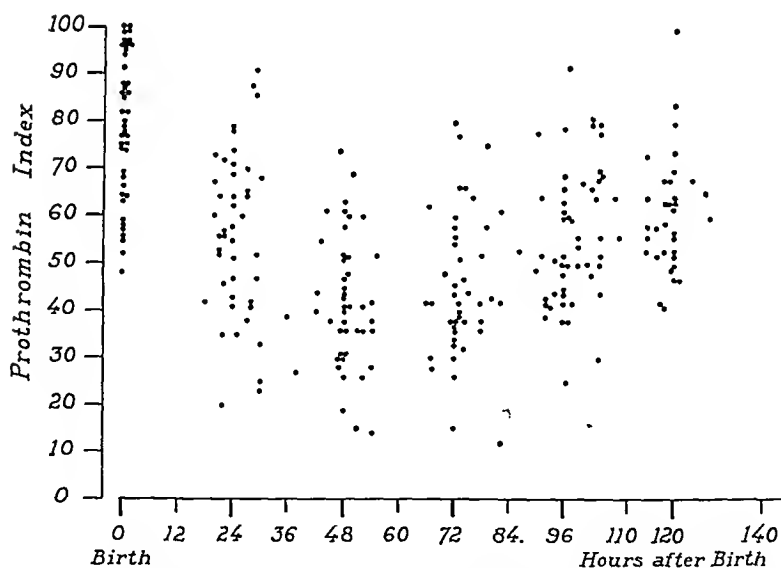
Fig. 6.—Elongated cells with scanty cytoplasm and oval nuclei rich in chromatin. Small capillary vessels are numerous.

it will be noted that the average of the initial indices was 80.2 per cent for the untreated group and 78.2 for the group of infants who received the blood injections. The lowest average value was 37.2 per cent for the untreated group and 39.3 for the treated group. The average final value, at the end of five days, was 61.2 for the un-



*Babies on Breast Only*

Fig. 1.



*Babies on Breast - Given 20cc. Maternal Blood Intramuscularly*

Fig. 2.

treated group and 61.6 for the treated group. These trends were generally alike with only slight advantages in favor of the group of infants who received the injections of blood. The figures of this table are shown graphically in Fig. 3.

The number of infants who regained their initial prothrombin levels and the number who reached 100 per cent by the end of five days were approximately the same in the two groups (Table II).

# THE EFFECT OF INTRAMUSCULAR INJECTIONS OF WHOLE BLOOD ON THE PROTHROMBIN INDEX OF THE NEWBORN INFANT

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THE value of intramuscular injections of whole blood in the prevention and treatment of hemorrhagic disease of the newborn infant has been questioned for many years. The history of this therapeutic procedure has been reviewed by Sanford and Leslie<sup>1</sup> and Quick and Grossman.<sup>2</sup>

Now that the majority of hemorrhagic diseases of the neonatal period have been shown to be due to deficiencies of prothrombin, it is important to measure the influence of intramuscular injections of blood upon the prothrombin indices.

Lawson<sup>3</sup> has recently reviewed the subject and contributed experimental evidence of the inadequacy of such intramuscular injections in raising the prothrombin levels. He reported that ten newborn infants who received intramuscular injections of their mothers' blood had levels of prothrombin during the first ten days of life which were comparable to those of ten other infants who had received no such injections.

## PROCEDURE

The prothrombin clotting time was determined by the micro-technique devised by Kato as a modification of the Quick method.<sup>4</sup> The values were expressed in terms of prothrombin index, derived from the formula

$$\frac{\text{Normal clotting time}}{\text{Infant's clotting time}} \times 100 = \text{Prothrombin index.}$$

The blood was collected in small test tubes 7 mm. in internal diameter and 15 mm. in length instead of ground glass hollow slides. The thromboplastin\* was extracted from rabbit's brain. Normal clotting time by the Kato method was  $20 \pm 2$  seconds.

The initial prothrombin determination was made within an hour or two after the infant was born and on each of the next five days. All of the infants received the same type of feeding during the neonatal period. They were put at the breast for the first time when they were twelve hours old and at intervals of four hours thereafter.

## RESULTS

The first group of 35 infants who received no injection of blood had prothrombin indices which are shown in Fig. 1.

The second group of 44 infants received 20 c.c. of their mothers' blood by intramuscular injection immediately after the first prothrombin determination was made. Their prothrombin indices are shown in Fig. 2.

To summarize these observations, averages were determined of the initial values of the prothrombin index, of the lowest values, and of the final values. In Table I,

\*The thromboplastin was supplied by The Difco Co.

When the changes in prothrombin indices were calculated in terms of the initial values, it was found that the untreated group of infants lost an average of 52.3 per cent of their initial values and returned to 78.3 per cent within the five-day period of observation. The group of infants who had received the injections of blood lost an average of 49.1 per cent of their initial values and returned to 81.3 per cent during the same period of time. The differences between the two groups was not striking (Table III).

#### SUMMARY

The prothrombin indices of 78 newborn breast-fed infants were determined for the first five days of life. Forty-four of these infants received intramuscular injections of whole blood and 35 did not. When the prothrombin indices of the two groups were compared, it was observed that a single intramuscular injection of 20 c.c. of maternal blood had little or no effect in checking the decline of the prothrombin index during the neonatal period, or in hastening its return to normal values.

#### REFERENCES

- (1) *Sanford, H. N., and Leslie, E. I.*: J. Pediat. 12: 16, 1938. (2) *Quick, A. J., and Grossman, A. M.*: Am. J. M. Sc. 199: 1, 1940. (3) *Lawson, R. B.*: J. Pediat. 18: 224, 1941. (4) *Kato, K.*: Am. J. Clin. Path. 10: 147, 1940.

## A PRIMARY TUBAL CARCINOMA ASSOCIATED WITH A PRIMARY OVARIAN SARCOMA

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PRIMARY carcinoma of the Fallopian tubes still stands as a gynecologic rarity. Though Renaud<sup>1</sup> called attention to this affection of the Fallopian tubes in 1847, it was probably Orthmann<sup>2</sup> who, in 1888, gave the first accurate pathologic description of this type of cancer. According to Baron<sup>3</sup> there were 363 cases of primary tubal carcinoma reported in the literature up to February, 1939. The incidence of primary tubal carcinoma is probably one in five to ten thousand gynecologic admissions. There has been only one other case of primary carcinoma of the Fallopian tube recorded in the files of John Sealy Hospital during the period from July, 1920, to July, 1940, from a total of 11,300 gynecologic admissions.

In making this report, we are adding another case of primary tubal carcinoma to the literature, but of greater interest is the fact that it was associated with a primary ovarian sarcoma. We are unable to discover the report of a similar case in the literature, and we offer no speculation as to why these two types of rare malignancy should occur together in the same individual.

CASE RECORD.—Patient F. C., a 39-year-old married negro woman entered John Sealy Hospital on March 22, 1940, complaining of soreness and a dull aching pain in the lower abdomen. Her symptoms had been present for only three weeks during which time she had been conscious of a mass in the lower abdomen. For twelve months the patient had experienced a watery vaginal discharge which necessitated the wearing of a pad most of the time. She claims to have lost 50 pounds during the eighteen-month period preceding her hospital admission, though she weighed 180 pounds on admission and showed no signs of recent loss. She had never experienced urinary or gastrointestinal symptoms, and she denied symptoms referable to the

TABLE I. PROTHROMBIN INDICES IN 2 GROUPS OF INFANTS

	AVERAGE PROTHROMBIN INDEX		
	FIRST VALUE	LOWEST VALUE	FINAL VALUE
Group 1: 35 infants Untreated	80.2	37.2	61.2
Group 2: 44 infants Received 20 c.c. of whole blood, intramuscularly	78.2	39.3	61.6

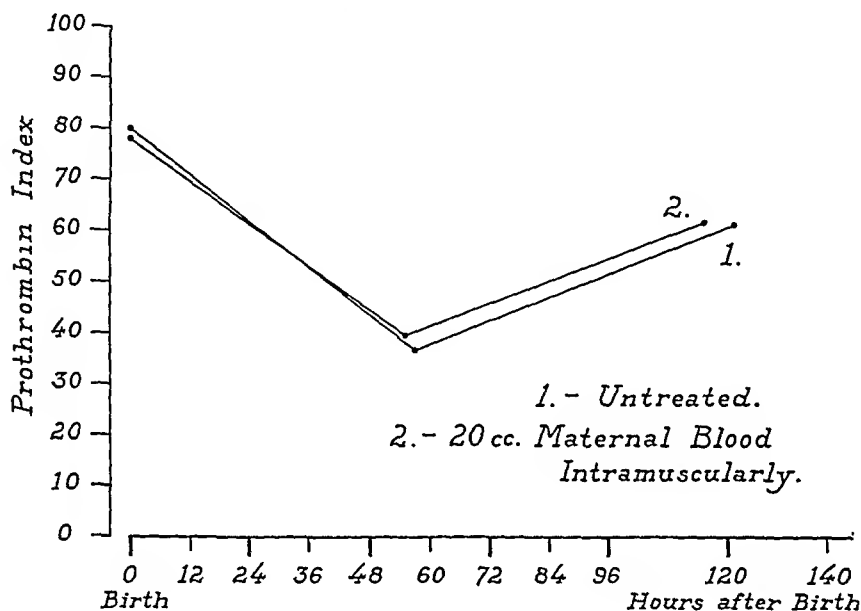


Fig. 3.

TABLE II. PATIENTS REGAINING INITIAL VALUES AND REACHING 100 PER CENT OF NORMAL WITHIN FIVE DAYS

	REGAINED INITIAL VALUE	REACHED 100%
Group 1: 35 infants Untreated	9	0
Group 2: 44 infants Received 20 c.c. of whole blood, intramuscularly	8	1

TABLE III. CHANGE IN PROTHROMBIN INDEX CALCULATED AS PERCENTAGE OF INITIAL VALUE

	MAXIMUM LOSS AS % OF INITIAL VALUE	FINAL VALUES AS % OF INITIAL VALUE
Group 1: 35 infants Untreated	52.3	78.3
Group 2: 44 infants Received 20 c.c. of whole blood, intramuscularly	49.1	81.3

depth. There was a papillary mass of grayish red, somewhat necrotic tissue, extending downward from the right cornual area of the uterine cavity. This mass measured 33 by 10 by 5 mm. and was attached at various points to the endometrium. It protruded through the endocervical canal. Careful dissection of the right lateral angle of the uterus and the isthmus of the tube showed the papillary growth to be continuous with a large right intratubal mass. The right tube was markedly dilated throughout its entire length and measured 16 by 11 by 7 cm. in size. Its surface was gray and smooth except for a few fibrinous and fibrous adhesions. In places the wall of the tube was so thinned that perforations had occurred, and through these perforations gray necrotic tissue protruded. Cut section of the tube showed it to be completely filled with grayish pink necrotic tissue. Numerous small hemorrhages and areas of yellowish-orange necrotic tissue were scattered throughout the tumor. In places this mass was firmly attached to the inner wall of the Fallopian tube. In other regions it merely dilated the tube but was not definitely attached. Various transverse sections of the tube showed this tumor to pass through the lumen of the tube and into the uterine cavity, where it was implanted on the endometrium. The fimbriated end of the tube was sealed by fibrous adhesions.

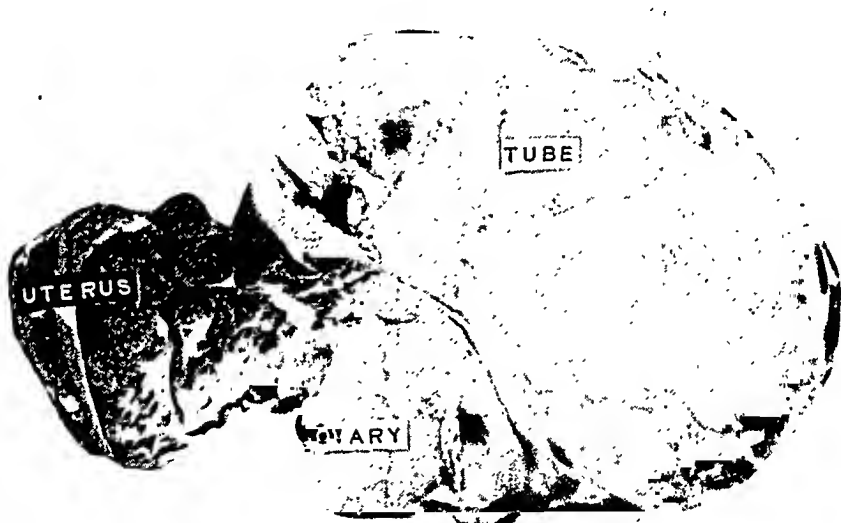


Fig. 1.—Uterus, carcinomatous right Fallopian tube, and sarcomatous right ovary viewed from the posterior side.

The right ovary was attached to the tubal mass by adhesions though separation was not difficult, the adhesions being friable and easily torn. The right ovary measured 5½ by 4 by 4 cm. and was mealy gray in color. It had an irregular consistency from firm to pultaceous. Cut section revealed several cavities that were filled with a thin milky fluid.

The left tube and ovary appeared normal, except for surrounding fibrinous and fibrous adhesions.

*Microscopic Findings.*—Examination of the right Fallopian tube showed it to be lined with a columnar and pseudostratified columnar epithelium. Numerous small and large papillary projections extended in all directions and completely filled the tube. In places they were compressed together and formed solid bands of epithelium with some tendency toward acini formation. Towards the central portion of the tube the tumor had apparently outgrown its blood supply, and the tissue was completely necrotic. The individual cells were generally large columnar, but varied markedly in both size and shape. Numerous mitotic figures were present, as many as four to eight being present in a single high power field. The nuclei, most of which were oval shaped, contained large amounts of diffusely scattered nuclear

abdominal or pelvic regions prior to her present illness. Of interest is the patient's menstrual history. Her last menstrual flow was ten weeks before her hospital admission. This was an interval of complete amenorrhea, not even a spotting of blood had been present. Her menses prior to this time had been regular in all particulars: onset at thirteen years, interval thirty days, duration four to five days. Her obstetric history showed one pregnancy ten years previously, terminating in a spontaneous abortion at four and one-half months.

Physical examination on admission revealed an obese colored female about the stated age, not apparently ill. Her temperature was 99.4° F., pulse 90, blood pressure 136/90. A large abdominal tumor was obvious, and some lower abdominal tenderness was present. Vaginal examination revealed a nulliparous introitus. The cervix was enlarged, soft, and boggy. It was smooth, symmetrical, and well epithelized. Lying in the cervical canal were particles of friable gray tissue. Bleeding occurred when a portion of this tissue was removed for histologic examination. The body of the uterus could not be defined as an independent mass. It seemed to be replaced by a hard fixed multinodular mass, which extended into each iliac fossa and to the level of the umbilicus. We felt that the patient had fibromyomas complicated by some type of degeneration or abortion, however pathologic examination of the tissue removed from the cervical canal revealed a glandular type of carcinoma which was interpreted as being adenocarcinoma of the body of the uterus.

*Laboratory Findings.*—The urine revealed rare red blood cells and frequent pus cells with clumping. Blood studies showed: hemoglobin 8.0 Gm.; red blood count 3,600,000; white blood count 7,900. The differential count was 79 per cent polymorphonuclear leucocytes, 18 per cent lymphocytes, and 3 per cent monocytes. An anteroposterior roentgenogram of the abdomen revealed a tumor mass to be somewhat eccentrically placed on the left side. In the lateral view a rounded tumor mass, having the appearance of a fibroid, was seen above the pelvic brim.

*Operation and Findings.*—The cervix was closed by suturing, preliminary to opening the abdomen. The peritoneal cavity was found to contain much old hemolyzed and clotted blood. A large, kidney-shaped tuboovarian mass (carcinoma) filled the lower abdomen. The mass apparently arose from the right side of the uterus but turned back and over the fundus, practically concealing the uterus. The mass was in contiguity with the entire right side of the moderately enlarged uterus, and was firmly adherent over a broad area to the floor of the right pelvis, as an intraligamentous tumor. There were several perforations in this large semisolid mass, through which much friable tissue passed when only slight pressure was made on its surface. There was another mass (sarcoma) lying posterior to the larger one, and it contained soft pulsatious areas which were easily broken into. A thin milky fluid extruded. No lymphatic metastases were demonstrable, and the firm clots filling the abdomen made it difficult to ascertain the presence or absence of established peritoneal growths. The operation consisted of a bilateral salpingo-oophorectomy, a supravaginal hysterectomy, and excision of a portion of adherent omentum. Removal of the cervix was thought inadvisable. Hemostasis was difficult because of the friability and vascularity of tissues. The abdomen was closed without drainage.

The patient was given 600 c.c. of citrated blood following the operation. Her postoperative course was essentially uneventful. On the eleventh postoperative day, intensive deep x-ray therapy was started. Six weeks following the operation viable cancer tissue was found at the external cervical os, so 3,000 mg. hours of radium was given by tandem into the cervical canal. The patient was in good health at the end of twelve months and was showing no evidence of recurrence. We consider her chances for a five-year survival practically nil.

#### PATHOLOGIC REPORT

*Gross.*—The specimen consisted of a supravaginally amputated uterus and both adnexa. The uterus measured 7 by 5½ by 4½ cm. The surface was covered with fibrous adhesions. The endometrium was thickened, measuring 6 mm. in its greatest



and occluded the lumen of the isthmus. A section through the uterus showed that the tumor had implanted on, and infiltrated into, the endometrium. The endometrial lymphatics were involved. The islands and strands of tumor cells in the uterus were similar to those seen in the Fallopian tube. The central part of the uterine papillary outgrowths was necrotic and round laminated deposits of calcium were present. A

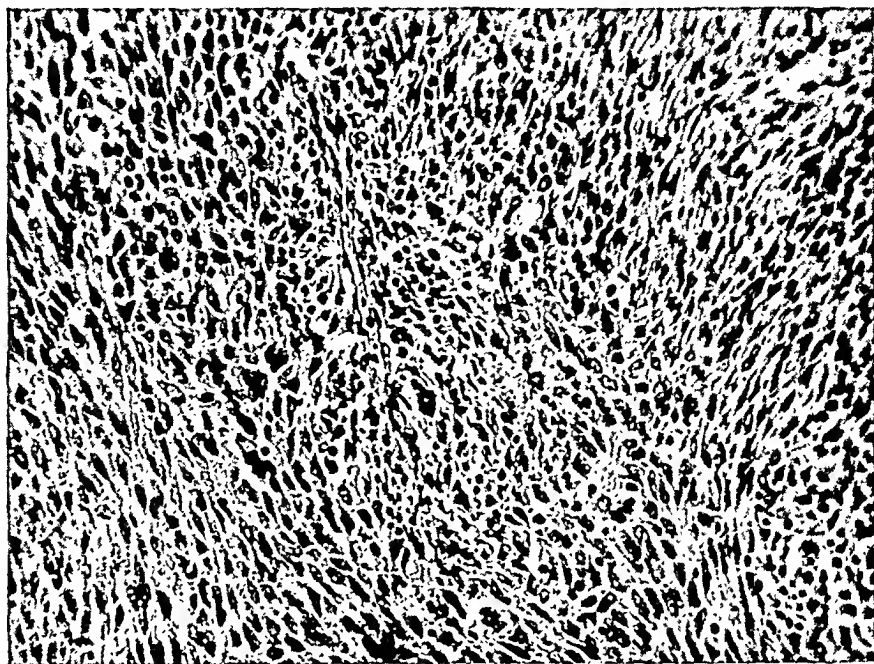


Fig. 4.—Low power of the sarcomatous right ovary. Note the tendency to form strands.

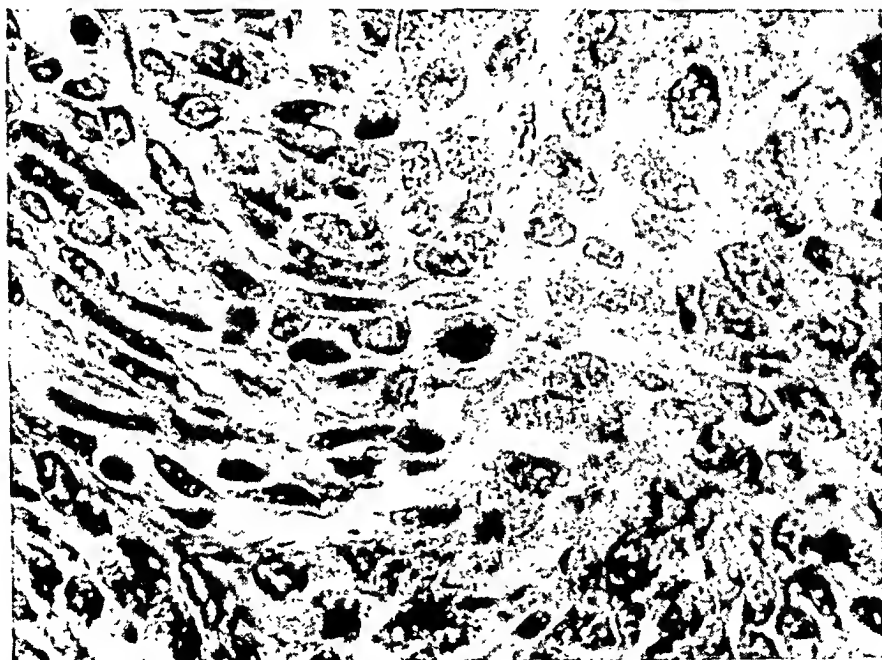


Fig. 5.—High power of the polymorphous cell sarcoma of the right ovary. The cells are large, spindle, and spheroidal shaped. Notice the numerous mitotic figures.

material and large nucleoli. There was very little stroma present. Thin-walled blood vessels were numerous. A section of the tube through the isthmus showed a picture similar to that seen in the distal portions. The growth protruded into

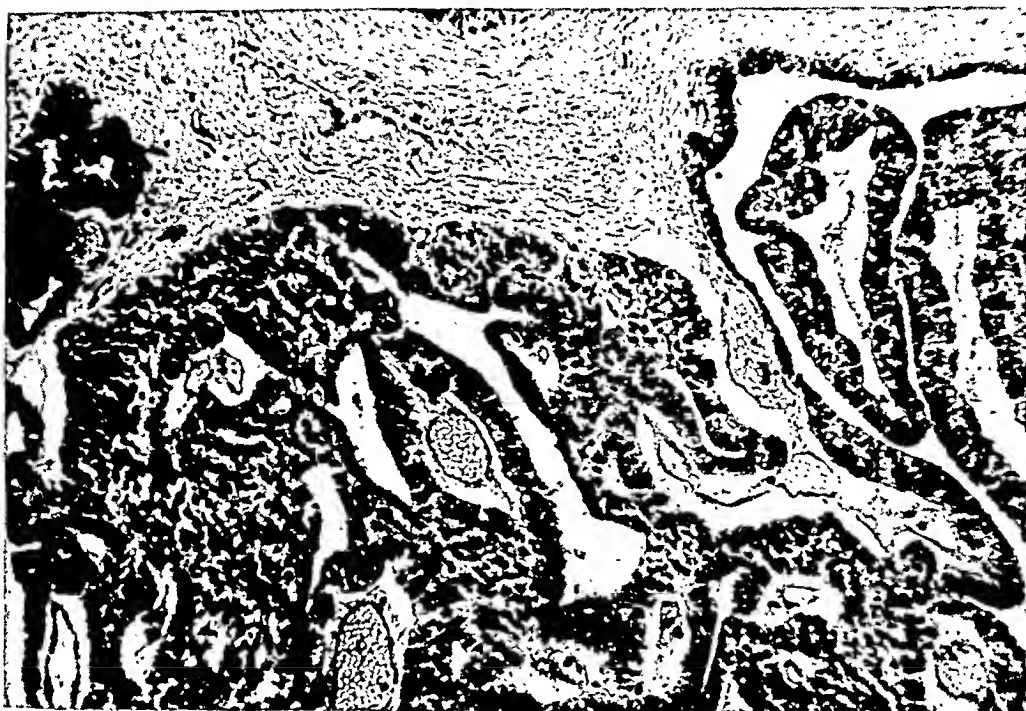


Fig. 2.—Low power of right Fallopian tube showing papillary out-growths of the carcinoma tissue.

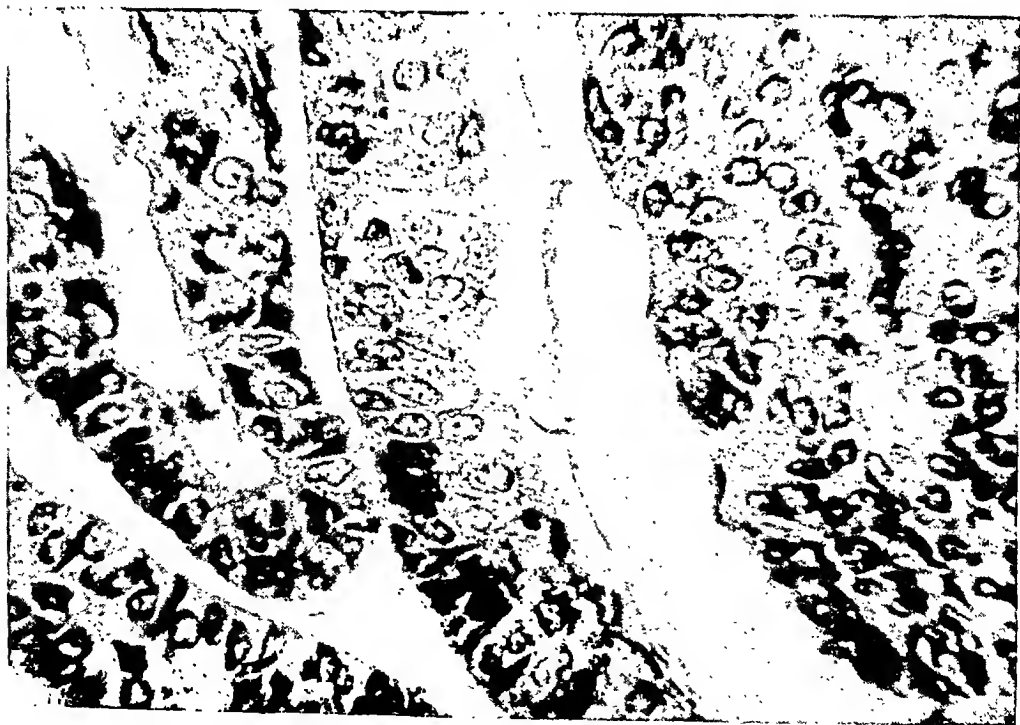


Fig. 3.—High power of the papillary carcinoma of the right Fallopian tube. Marked variation in size and shape of the cells is evident.

## INHIBITION OF LACTATION WITH STILBESTROL

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PRIOR to the synthesis of stilbestrol the suppression of lactation was frequently painful and difficult to accomplish. This study deals with the administration of stilbestrol orally in order to determine its efficacy in inhibiting lactation.

Fifty-five cases, 44 of which were primigravidas, requiring drying of the breasts were selected. Indications for the suppression of lactation were death of the fetus, breast abscess, sore nipples, etc.

Three nursing patients with severe painful engorgement were also given stilbestrol.

During the period of treatment, the patient's fluid intake was not restricted, tight binders were not employed and strong purgation was omitted.

### METHOD OF ADMINISTRATION AND RESULTS

We administered 5 mg. of stilbestrol once a day for four days to 26 patients, beginning the first post-partum day before engorgement had taken place. In these cases this dosage seemed sufficient. No nausea, no increase of lochia, or other side effects were noted in this group of patients. After four days of drug therapy, the breasts were soft and not painful. In a few cases a thin watery secretion was noted, but the results were considered satisfactory.

One interesting case was a patient with diabetes mellitus whose daily insulin requirement was not affected by the use of stilbestrol. This patient was a 20-year-old severe juvenile type of diabetic whose daily insulin requirement was 40 units of protamine zinc insulin. She received 5 mg. of stilbestrol daily for four days.

No medication was administered until engorgement or lactation had taken place in 29 patients. In these cases, the average dose of stilbestrol was 5 mg. twice a day for two days followed by 5 mg. daily for two days.

In one case severe nausea and vomiting was noted after 20 mg. of the drug had been administered, necessitating discontinuation of the drug. This patient had developed a breast abscess three weeks post partum. It is interesting to note that she had suffered from nausea and vomiting to some degree throughout her entire pregnancy.

Five patients who had received infusions of glucose and three with unilateral abscess of the breast responded satisfactorily only after receiving subsequent doses of stilbestrol of 5 mg. once a day for four days.

One patient eight months post partum responded satisfactorily after 60 mg. of stilbestrol had been given. In this case engorgement subsided in thirty-six hours, pain disappeared in forty-eight hours, and complete suppression of lactation occurred in six days without any toxic symptoms.

In this group there were 3 patients who had shown signs of toxemia of pregnancy or pre-eclampsia before delivery. In none of these patients could we find any toxic effects from the drug. One of these patients received the average dose of stilbestrol from the third through the sixth post-partum day with good results. On the tenth

few fairly normal endometrial glands were present, but even these showed marked dilatation and evidence of hyperplasia.

The right ovary was composed of tissue that was entirely different from the tubal carcinoma. Running in all directions were strands of large spindle- and spheroidal-shaped cells. The nuclei contained varying amounts of nuclear material and enlarged nucleoli. Mitotic figures were numerous, there being 6 to 10 present in some high power fields. The stroma was very scarce, the entire ovary being made up of malignant cells. Numerous thin-walled blood vessels were present and in places only a single layer of edematous endothelium was present. At one point the carcinoma of the tube had invaded the sarcoma of the ovary.

The left tube and ovary were essentially normal histologically.

#### COMMENT

Two rare malignant tumors, a primary carcinoma of the right Fallopian tube, and a primary sarcoma of the right ovary were coexistent. To our knowledge this is the first time that this combination of malignancies has been reported.

Contrary to the usual route of spread, the carcinoma of the Fallopian tube had grown from the tube into the uterine cavity and had become implanted on the endometrium and on the mucosa of the endocervix. The carcinoma involved the lymphatics of the tube and uterus in a few isolated areas. By direct extension it had infiltrated the sarcomatous right ovary.

The microscopic picture of the carcinoma was that of a papillary type, but in the more compressed areas it had an alveolar arrangement. This agrees with Liang's<sup>4</sup> belief that both the papillary and the papilloalveolar type are the same morphologic tumor.

The polymorphous cell sarcoma of the right ovary was highly malignant, and the entire ovary was involved. The predominating cell was spindle-shaped, with the other cells varying markedly in both size and shape.

We wish to express our appreciation to Dr. L. L. Griffin and Dr. Gus Eckhardt for their aid with the photomicrographs.

#### REFERENCES

- (1) *Renaud*, quoted by *Doran*: Tr. Path. Soc. London 39: 208, 1888. (2) *Orthmann*: Ztschr. f. Geburtsh. u. Gynäk. 15: 212, 1888. (3) *Baron, Henry A.*: Canad. M. A. J. 43: 118, 1940. (4) *Liang, Zue*: Virchows Arch. f. Path. Anat. 259: 577, 1926.

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**Rutherford, Robert N.**: Pseudocyesis, New England J. Med. 224: 639, 1941.

The author concludes a general study of the subject of spurious or imaginary pregnancy and a report of seven cases observed in Boston Lying-in Hospital during the last thirteen years with the following summary:

Pseudocyesis is a clinical entity that has existed unchanged in its symptomatology since Hippocrates first described it. Explanations of etiology mirror the medical thought of each generation, from the old physiologic explanation of "wind in the womb" to the newer concept that places the syndrome on a physiologic basis. The only additional aids to diagnosis have been the employment of roentgenography and of the biologic tests of pregnancy. Neither of these supersedes caution of the physician in diagnosing pregnancy. Today's treatment is identical with that of our medical forbears, except that it is garnished with psychotherapy.

HUGO EHRENFEST

2. An average dose of 20 mg. in the nonengorged breasts and 30 mg. after engorgement or lactation appeared to give satisfactory results without supportive treatment in 81 per cent of the cases.

3. Some complicated cases (17 per cent) will require additional therapy with the drug.

4. Nausea and vomiting in one case (2 per cent) was the only toxic effect of the drug noted.

5. Stilbestrol will alleviate pain and engorgement in the nursing mother without inhibiting lactation.

6. Pre-eclampsia and toxemia of pregnancy before delivery do not contraindicate the use of stilbestrol.

7. In one case, stilbestrol did not affect the daily insulin requirement of a severe diabetic patient.

Stilbestrol supplied through the courtesy of Eli Lilly Co.

#### REFERENCES

- (1) Abarbanel, A. R., and Goodfriend, M. J.: *AM. J. OBST. & GYNEC.* 40: 1037, 1940. (2) Mazer, C., Israel, S. L., and Ravetz, E.: *J. A. M. A.* 116: 675, 1941.

## A ROENTGENOLOGIC SIGN FOR THE DETECTION OF PLACENTA PREVIA

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THE location of the placenta has been shown ante partum with the aid of roentgenography in the following manner: (1) by the injection of absorbable radiopaque media into the amniotic cavity;<sup>1-3</sup> (2) by the injection of colloidal thorium dioxide intravenously;<sup>4, 5</sup> (3) by the use of radiopaque media in the urinary bladder;<sup>6-12</sup> and (4) by roentgenograms of the abdomen to show the soft tissue shadows of the uterus which may be combined with the injection of air into the urinary bladder or rectum.<sup>13-18</sup> The first two procedures should not be used on human beings, because in (1) abortions are produced, and in (2) the radioactive substance is not eliminated from the body.

The roentgen sign herein reported is based on the fact that a fetal head will dip into the pelvic inlet and occupy the midsagittal and mid-coronal planes of the superior strait when the mother is standing. It is applicable only in cases with a single fetus in cephalic presentation. This will include about 95 per cent of pregnancies. Any pelvic tumor mass of sufficient size can displace the fetal head from the mid-coronal or midsagittal plane or prevent it from dipping below the level of the brim of the inlet. Such a mass might be a uterine fibroid, an ovarian cyst, an overdistended bladder or rectum, or the placenta implanted low in the uterus. All except the latter can be ruled out by the usual methods of examination.

post-partum day, however, she developed an acute mastitis with a sudden rise in temperature to 104° F. Stilbestrol was given again for a total of 50 mg., during the next eight days. The mastitis subsided completely. This patient, therefore, received 80 mg. of stilbestrol without any toxic symptoms, despite the fact that she was a pre-eclamptic before delivery.

It was observed, also, that 8 other patients with breast abscesses required no larger dose of stilbestrol than the average. Therefore, in this group there were 21 cases in which complete drying of the breasts was carried out to our satisfaction on the average amount of stilbestrol.

In 3 cases of severe engorgement and painful breasts in the nursing mother, we administered 5 mg. of stilbestrol for two days. In these cases engorgement and pain rapidly subsided but lactation continued. Although this group is small, it seems to indicate that stilbestrol will not stop lactation in the nursing mother and is useful in painfully engorged breasts.

### DISCUSSION

The dose of stilbestrol selected was arbitrary and was not based on any previous experience with the drug. Enseals and tablets were used at random. We noted that the 5 mg. tablets originally supplied for clinical investigation were apparently more efficacious than a total of five 1 mg. tablets.

Our cases included both white and colored patients from the obstetric ward of the hospital and the home delivery service. Several of our cases were complicated with high fevers due to pyelitis, upper respiratory infections, etc., but this did not seem to influence the effect and value of the drug. All of our patients have been followed up for a period ranging from one to five months.

### SUMMARY

Fifty-five cases have been presented in which stilbestrol was used to inhibit or stop lactation both before and after lactation had occurred. In the average cases, a total of 20 mg. was used in the nonengorged and 30 mg. in the engorged or lactating breasts. The end results of both procedures were satisfactory. Abscess formation in the engorged breasts, as well as excessive amounts of fluid by the intravenous route and prolonged lactation, seemed to necessitate an additional amount of drug therapy.

Three cases of severe painful engorgement of the breasts in the nursing mother responded favorably to 10 mg. of the drug without inhibiting lactation.

In one case of a severe juvenile diabetic, the administration of stilbestrol did not affect the insulin requirement. Since the report of the use of estrin to reduce the insulin requirements of diabetics, further study of the effects of stilbestrol (synthetic estrin) on diabetic patients will be interesting to observe.

### CONCLUSION

1. Stilbestrol by the oral route has been efficacious in 54 cases (98 per cent) to inhibit lactation.

In roentgenograms taken during the last ten to twelve weeks of gestation, by the technique described, the fetal head will be found normally in the midsagittal and midcoronal planes of the superior strait, and, even if not engaged, it will be dipping below the level of the brim of the true pelvis (Fig. 1 and 2). When the fetal head is not found in either the midsagittal or midcoronal planes and the lowest point

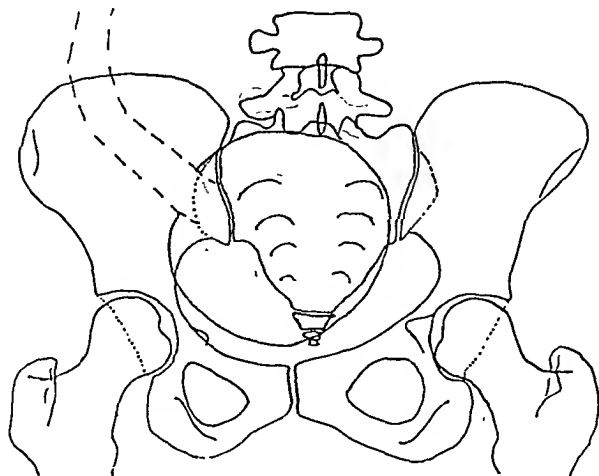


Fig. 3.

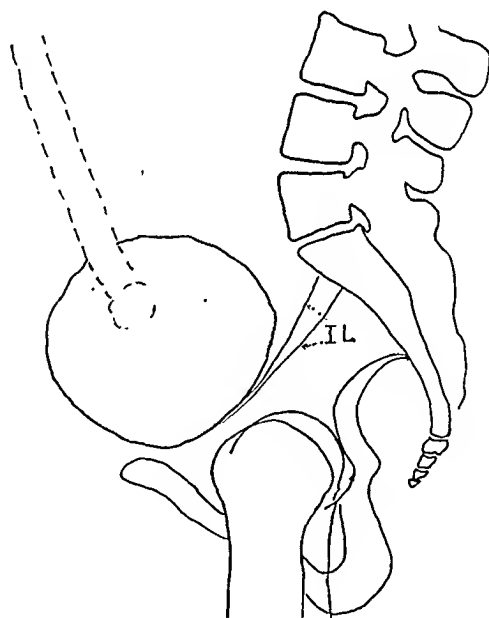


Fig. 4.

Figs. 3 and 4.—Traecings of roentgenograms taken in anteroposterior and lateral views of a woman in the fortieth week of gestation standing erect. There was no history of vaginal bleeding.

The position of the fetal head, displaced to the right of the midline and not dipping below the inlet, suggested the presence of a pelvic tumor mass.

The patient was delivered by cesarean section. The placenta was found lying over the internal os of the cervix. I L is the ileocecal line, indicating the plane of the pelvic inlet.

of the fetal skull is at or above the level of the pelvic inlet, it indicates a displacement by a soft tissue mass in the pelvis (Figs. 3 and 4). If the pelvic mass is not due to a fibroid, ovarian cyst, or overdistended sigmoid or urinary bladder, it may be a low implantation of the placenta (placenta previa).

## TECHNIQUE OF EXAMINATION

Roentgenograms of the pelvis are taken in anteroposterior and lateral views with the patient standing. A vertical Potter-Bucky diaphragm is used. A convenient anode-film distance is 36 inches. Cassettes holding 14 by 17 inch films are used in order to include the shadow of the fetus and uterus. In the lateral view the central

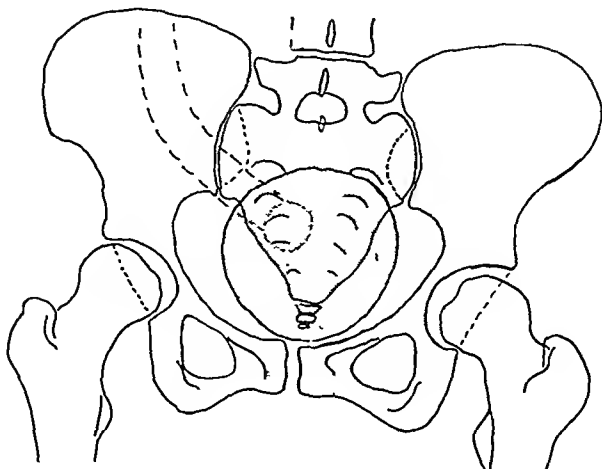


Fig. 1.

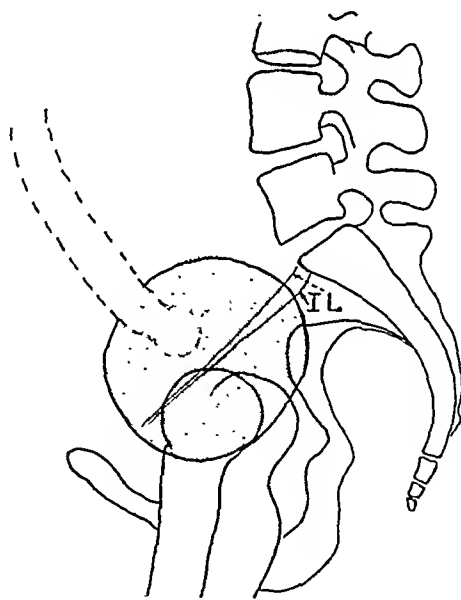


Fig. 2.

Figs. 1 and 2.—Tracings of roentgenograms taken in anteroposterior and lateral views of a woman in the thirtieth week of gestation standing erect. There was a history of recent vaginal bleeding. The position of the fetal head, dipping below the brim of the true pelvis and in the midsagittal and midcoronal planes, excluded the presence of a placenta previa. The position of the fetal head shown in 1 and 2 is the usual finding in roentgenograms taken with the patient standing. I L is the ileopectineal line, indicating the plane of the pelvic inlet.

rays are directed through the superior border of the acetabulum. The patient then turns 20 degrees to face the x-ray tube for the anteroposterior view. The Potter-Bucky diaphragm and tube, when not changed, are at the proper height for the second exposure. The central rays for the exposure should pass through the midsagittal plane of the pelvis. The technique is the same as that used in taking films for pelvimetry and fetal cephalometry.



## TWIN PREGNANCY IN THE RUDIMENTARY HORN OF A BICORNUATE UTERUS ASSOCIATED WITH RENAL AGENESIS

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THE patient, M. S. (236083), aged 26 years, had frequented the Outpatient Department since 1933, complaining of alternate periods of hypomenorrhea and amenorrhea. Several times the diagnosis of right ovarian cyst or right ectopic pregnancy had been made, but the diagnosis disqualified on further investigation. In June, 1939, a diagnosis of pregnancy was verified by the Friedman test. The date of expected labor was estimated for September 22. In September, however, the uterus was found to be only the size of an eight months' pregnancy. Her prenatal course had been uneventful until the October visit, at which time fetal heart tones were no longer heard, the patient began to lose weight and developed a two-to three-plus albuminuria, unaccompanied by hypertension. A flat plate of the abdomen revealed two fetal heads but only one fetal spine. On October 28, she began to spot vaginally, but since the spotting was not associated with pain she deferred entering the hospital until two days later. The only relevant notes in her past history were that she had had scarlet fever in her childhood and that she had received, in 1934, stimulating doses of x-ray to her ovaries and had received thyroid and ovarian substance in 1933 to 1935 for hypomenorrhea.

Examination on admission revealed a well-developed, well-nourished white female not in active labor. Temperature, pulse, and respiration were normal. Blood pressure was 128/88. Her head and neck showed no abnormalities; the lungs were clear; the heart appeared normal. In the abdomen, the uterus was the size of an eight months' pregnancy. It was quite tense but not tender. One was unable to outline definitely fetal position. No fetal heart tones were heard. Rectal examination offered no diagnostic assistance, inasmuch as both the presenting part and the cervix were out of reach. A cystogram was done and apparently was negative for placenta previa; it did, however, show two fetal heads but visualized only one fetal spine.

On October 31, the patient passed a piece of tissue grossly resembling placenta. Microscopic section revealed decidual tissue, but no chorionic villi were found. Fetal heart tones were not heard. An electrocardiogram showed no fetal heart beats. Repeated x-rays failed to reveal the second fetal spine. A sterile vaginal examination disclosed an unfavorable cervix about one inch long, which admitted only a fingertip. The presenting breech was found dipping into the inlet. No bleeding followed the vaginal examination. A medical induction, consisting of castor oil, quinine, and an enema, failed. On November 3, the Friedman test was reported as negative. When, on the next day, a repetition of the medical induction was ineffective, rupture of the bag of waters was decided upon. A sterile vaginal examination again revealed an uneffaced cervix admitting no more than the tip of one finger. The bimanual examination was confusing. A hard, fixed mass was felt on the right; a movable mass was felt on the left. An Allis forceps could not be passed beyond  $1\frac{1}{2}$  inches, and the examiner was unable to grasp membranes with the instrument. It was concluded that a mass was obstructing in the region of the internal os. On November 6, a flat plate of the abdomen finally revealed two heads and two fetal spines. On November 8, under gas anesthesia, the cervix was dilated with Hegar and Goodell dilators and a Voorhees' bag was inserted. The following day, the bag fell out but the

From our experience over a period of four years in examining roentgenograms of pregnant women, taken during the last trimester of gestation and with the patient erect, we believe any displacement of the fetal head from the midline is significant. We have accepted, for a tentative working basis, a linear displacement of one-third the diameter of the fetal head from its usual position (Fig. 1) to represent the presence of an abnormal pelvic mass. It may be that smaller degrees of displacement combined with the failure of the fetal head to dip into the superior strait will prove to be significant. One can definitely rule out the presence of a placenta previa when the fetal head is found dipping into the pelvic inlet and not displaced from the midcoronal or midsagittal planes.

## REFERENCES

- (1) Menecs, T. O., Miller, J. D., and Holly, L. E.: *Am. J. Roentgenol.* 24: 363, 1930. (2) Kerr, J. M., and Mackey, W. C.: *Tr. Edinburgh Obst. Soc.*, 1932-33, pp. 21-22. Quoted by Friedman and MacDonald.<sup>8</sup> (3) Picinelli, G., and Bertolotto, U.: *Quaderni Radiol.* 3: 15, 1938. *Abst. Year Book Radiol.* p. 257, 1939. (4) Ehrhardt, K.: *Zentralbl. f. Gynäk.* 56: 847, 1932. (5) Menville, L. J., and Ané, J. N.: *Proc. Soc. Exper. Biol. & Med.* 30: 28, 1932. (6) Ude, W. H., Weum, T. W., and Urner, J. A.: *Am. J. Roentgenol.* 31: 230, 1934. (7) Ude, W. H., and Urner, J. A.: *AM. J. OBST. & GYNEC.* 29: 667, 1935. (8) Friedman, J., and MacDonald, D. O.: *Canad. M. A. J.* 32: 12, 1935. (9) McDowell, J. F.: *AM. J. OBST. & GYNEC.* 33: 436, 1937. (10) Hall, S. C., Currin, F. W., and Lynch, J. F.: *Ibid.* 33: 625, 1937. (11) Beck, A. C., and Light, F. P.: *Ibid.* 35: 1028, 1938. (12) Leon, J.: *La Radiología en Obstetrica*, Chapter 7, "El Ateneo," Buenos Aires, 1940. (13) Snow, W., and Powell, C. B.: *Am. J. Roentgenol.* 31: 37, 1934. (14) Snow, W., and Rosensohn, M.: *Ibid.* 42: 709, 1939. (15) Weintraub, S., and Snow, W.: *Ibid.* 42: 718, 1939. (16) Snow, W.: *New York State J. Med.* 40: 2050, 1939. (17) Hodges, P. C., and Dippel, A. L.: *Surg., Gynec. & Obst.* 70: 421, 1940. (18) Dippel, A. L., and Brown, W. H.: *AM. J. OBST. & GYNEC.* 40: 986, 1940.

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Elliott, Gillespie, and Holland, Eardley: *An Outbreak of Pemphigus Neonatorum in a Maternity Home*, *Lancet* 1: 169, 1941.

An outbreak of skin infection resembling pemphigus neonatorum occurred in a maternity home: 22 infants, 2 mothers, and 1 nurse were affected.

Profuse, almost pure cultures of *Staph. pyogenes* were obtained from the lesions in 10 out of 11 cases examined bacteriologically and all were found to be type IIIc (Cowan).

A nurse who had two skin lesions was a nasal carrier of staphylococci of the same type. Staphylococci of this type were also recovered from plates exposed to the air during the outbreak in two wards in which were infected patients and in the nurses' dining room. These organisms were not isolated from the air of two unoccupied wards or a ward containing an uninfected patient. The evidence suggests that the nurse may have been the source and also the means of spread of the infection.

CARL P. HUBER

The laboratory findings during her period of hospitalization were as follows:

Nonprotein nitrogen ranged from 24.0 to 33.3 mg. per cent.

Urea nitrogen ranged from 16.8 to 28.6 mg. per cent.

Creatinine ranged from 1.5 to 1.7 mg. per cent.

Total protein ranged from 7.60 to 8.36 mg. per cent.

Albumin-globulin ratio ranged from 4.51/3.09 to 5.54/3.46.

Twenty-four-hour albumin ranged from 4.28 to 12.4 Gm.

Cholesterol ranged from 125 to 187 mg. per cent.

Uric acid was 3.4 mg. per cent.

Sedimentation rate varied from 112 to 134 mm. precipitation (Westergren) in two hours.

Hemoglobin varied from 12.5 to 13.5 Gm.

White blood count varied from 18,200 to 12,200.

Urinalysis: sugar negative; albumin varied from one-plus to four-plus.

This patient was seen in December, 1940, at which time a urologic check-up was done. Cystoscopy revealed the left ureteral orifice in normal position and functioning. There was no evidence of the right orifice. A No. 6 F. ureteral catheter was passed full length on the left, releasing 3 c.c. of clear residual urine. Indigo carmine appeared from the left side in three minutes with good concentration, but there was no evidence of the right orifice in the bladder or urethra. The flat plate of the abdomen and left retrograde pyelograms showed the left kidney somewhat enlarged; the right kidney was absent.

#### SUMMARY

Presented herewith, because of its rarity, is a case of twin pregnancy in the rudimentary horn of a bicornuate uterus with associated renal agenesis. Gestation had progressed to approximately seven months before fetal death occurred. The uterus was unusually refractory to all attempts at the induction of labor.

In retrospect, the lipiodol injection into the uterine cavity was a procedure open to criticism.

The case illustrates typically enough the extraordinary difficulty encountered in making a diagnosis of extrauterine pregnancy.

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## PREGNANCY COMPLICATING HODGKIN'S DISEASE (LYMPHOGRANULOMA MALIGNUM)

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THE incidence of pregnancy complicating Hodgkin's disease is of such unusual occurrence that the following case report was deemed worthy of presentation. There are only two other cases fully reported in the literature.<sup>1, 2</sup>

E. S. (Bronx Hospital No. 68772), white, Jewish, aged 27 years, was referred by her family physician for obstetric care in March, 1936. She had had one previous spontaneous full-term delivery with an uneventful puerperium in 1932. Her past medical and surgical history were irrelevant. Her pelvis was of the gynecoid type; physical examination, urine, and blood pressure were normal and the Wassermann reaction was negative. After a normal prenatal course she was delivered spontaneously on Aug. 13, 1936, after a seven-hour labor of a living male child, weighing 8 pounds. Her puerperium was not remarkable and she was discharged on Aug. 22, 1936.

She was not seen again until Oct. 30, 1937, when she was readmitted to Bronx Hospital (No. 82501) because of progressive glandular enlargements of the neck

\*Presented at a meeting of the Clinical Society of the Bronx Hospital, May 12, 1941.

patient was not in labor. Vaginal examination at that time revealed that the dilated cervix led into a small empty uterine cavity.

On November 11, lipiodol was injected into the uterine cavity. Pictures were of no diagnostic value. Following this procedure, the patient developed a febrile reaction.

On November 20, with a preoperative diagnosis of twin pregnancy, either extra-uterine or in an anomalous uterus, the patient was subjected to a laparotomy. A subtotal hysterectomy and a right salpingoophorectomy were performed.

A twin pregnancy was found in an appendage (rudimentary horn) which was attached to the right side of the main body of the uterus in the region of its internal os. The appendage measured 9 by 6 $\frac{3}{4}$  by 6 inches. Both fetuses were female, measured 26.5 cm. and 28.5 cm. in length, respectively, and were macerated. The umbilical cords measured 29 cm. and 25 cm. in length, respectively. The placental mass occupied most of the inner wall of the cavity. The wall of the appendage (rudimentary horn) measured 5 mm. in its thickest portion. Included in the specimen were a tube and ovary, the latter measuring 6.5 by 1.5 by 1.5 cm., which, on opening, revealed a cavity containing a small amount of red fluid blood. The uterus proper measured approximately 6.5 by 4.5 by 3.5 cm.

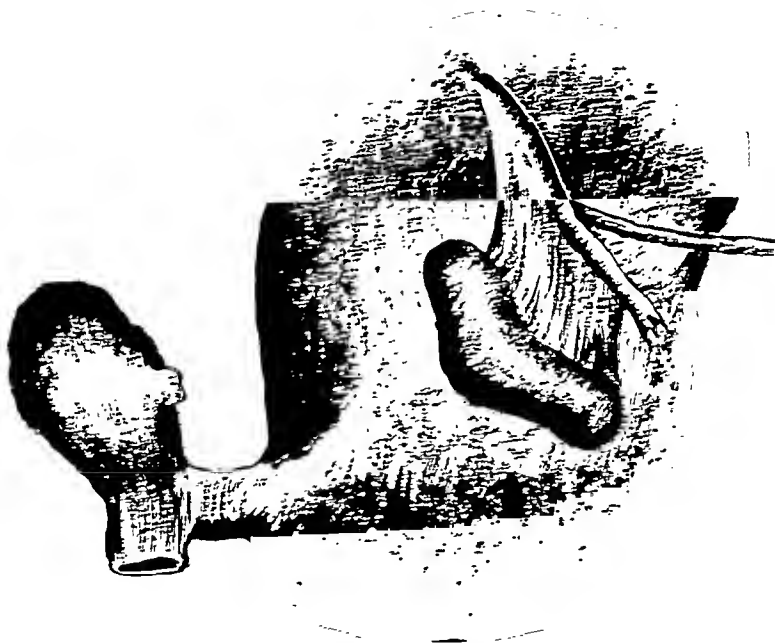


Fig 1.—Sketch of specimen viewed from behind, showing right tube and ovary and insertion of round ligament into rudimentary horn. The pedicle passes from the larger gravid to the nonpregnant organ.

Subserously, there were noted two hard nodular projections (fibroids), each of which measured approximately 1 cm. in diameter. The pedicle between the rudimentary horn and the uterus proper measured 3.5 cm. in length. Although no canal could be probed between the two, microscopic section revealed the presence of such communication. The round ligament on the left was attached to the uterus proper; on the right, it was attached to the anterior superior portion of the rudimentary horn. X-rays of the fetuses revealed osseous skeletal development corresponding to that of a 6 $\frac{1}{2}$  to seven months' fetus.

The postoperative course was uneventful until the tenth day, at which time she developed an embolus with a lung infarct in the left base. One week later, having been afebrile and asymptomatic for three days, she signed her release from the hospital. Intravenous pyelograms taken shortly before her discharge showed no ureteral shadow and no dye excretion on the right. The left kidney was fairly well outlined and appeared to be normal.

terian Hospital by request of the family, where she died nine days later. Necropsy confirmed generalized Hodgkin's disease (lymphogranuloma malignum).\*

Follow-up studies on the baby (because of the exposure to radiation), now two and one-half years old, showed a normal development for her age.

#### SUMMARY

A case of Hodgkin's disease is reported, complicated by a gravidity. The patient received radiation therapy during the early months of her pregnancy. A healthy child was born, whose subsequent development was normal.

I am indebted to Dr. Meyer Rosensohn for his advice in the preparation of this report, and to Dr. Joseph Felsen for the photomicrograph.

#### REFERENCES

- (1) *Davis, A. B.*: Bull. Lying-in Hospital 7: 151, 1911. (2) *Gemmell, A. A.*: J. Obst. & Gynaec. Brit. Emp. 30: 373, 1923.

## PLACENTA PREVIA IN THREE SUCCESSIVE PREGNANCIES

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MRS. C. G. P., aged 29 years, first consulted us on Nov. 7, 1934; her last menstruation had occurred on Sept. 14, 1934. Family history was irrelevant. She had had no previous pregnancies. Relevant in her past history was uterine bleeding which was treated unsuccessfully by two dilatations and curettages of the uterus but was successfully treated by implantation of 400 mg. hr. of radium. Her pregnancy was uncomplicated until Feb. 11, 1935, when the patient had slight, intermittent, bleeding for several months. About April 5, 1935, she developed hypertension and was kept in bed for six weeks. Spontaneous rupture of her membranes occurred on May 14, 1935, and she was hospitalized at the Norfolk General Hospital with the preoperative diagnosis of placenta previa, transverse position with ruptured membranes, and hypertension. A low cervical cesarean section was started under gas and local anesthesia. In separating the bladder from the uterus, the bladder was found to be attached intimately to the cervix and could not be separated. There were large dilated veins at this point. It was, therefore, impractical to do a typical low cervical section, so the incision was carried down to the point near the internal os from which the bladder was separable, and thence up high enough into the uterus to permit delivery of the baby. The eight months' baby was extracted by breech. He cried immediately and was placed in an incubator. The uterine wall was very thick, even down to the cervix, and gave the impression of a fibromyomatous uterus. A section of the uterus was removed for biopsy, and it showed fibrosis of the uterine muscle. After closure of the uterus, it contracted satisfactorily. The placenta had been located in the lower segment of the uterus entirely covering the cervix. Except for a few white infarcts, the placenta was grossly normal. The patient's puerperium was uncomplicated. The baby died. Autopsy showed only prematurity.

The patient continued well and became pregnant again, her last period being March 1, 1936. The pregnancy was uncomplicated until Oct. 18, 1936, when she noticed slight brownish spotting from the vagina without free bleeding. The spotting was controlled by bed rest until Oct. 23, 1936, when the patient was awakened by slight vaginal pain and found herself lying in a pool of fresh blood. She was hospitalized immediately and a modified low flap Beck cesarean section was done. The diagnosis of placenta previa with transverse lie and premature separation of the placenta was confirmed at operation. The placenta was centrally located over the internal os, and a large clot was found on its maternal surface. The 7 to 7½

\*Courtesy of Dr. William C. Von Glahn, Presbyterian Hospital.

and the left axilla during the past year, accompanied by severe itching of two weeks' duration. Positive findings on this examination were: Bilateral enlargements of the cervical and supraclavicular lymph nodes, the glands ranging in size from that of a pea to that of a small walnut. The glands were discrete and freely movable. There were also present enlarged nodes in the right axilla and left inguinal region. There was present a moderate secondary anemia with 66 per cent Hg and 4.0 million red blood cells, a mild leucocytosis of 13,000 with 80 per cent polymorphonuclears; and widening of the mediastinum by x-ray was noted.

A biopsy of one of the cervical nodes revealed Hodgkin's disease (lymphogranuloma malignum) (Path. No. 12785). Patient was discharged for radiation therapy.

During the next four weeks she received radiation consisting of 1,200 r. units in divided doses through  $\frac{1}{2}$  inch copper and 1 inch aluminum filter over neck and sternal regions. Her blood count remained stationary, but because of the amenorrhea and a suggestive enlargement of the uterus, a Friedman test was done, which was reported as positive. It was decided to let her continue her pregnancy because Hodgkin's disease would not preclude the development of a normal viable fetus, nor would this pregnancy endanger the life of the mother or aggravate the course of her disease.

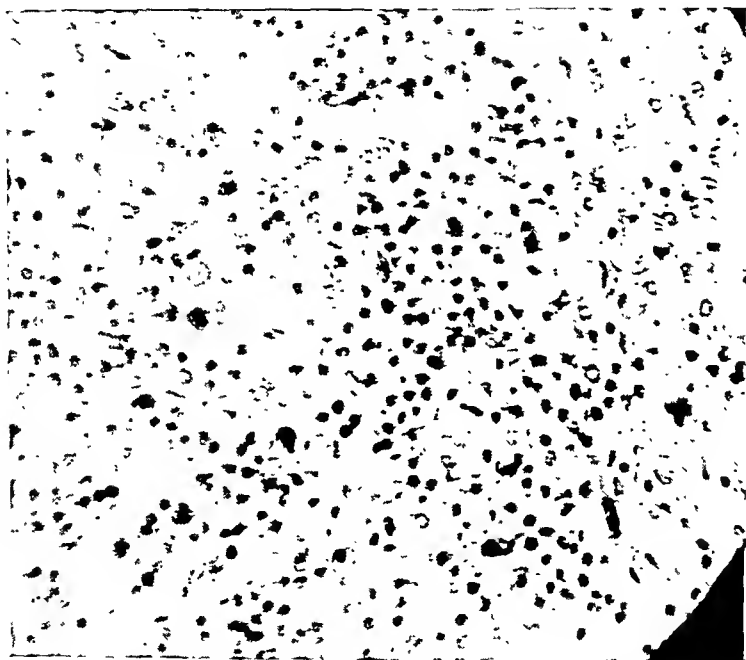


Fig. 1.—Cervical node, high power, showing the Dorothy Reed cells.

On Sept. 18, 1938, she had a spontaneous delivery of a 6 pound 2 ounce, living, normal female child. Her puerperium was uneventful and she was discharged on Sept. 27, 1938.

During the next two years, that is, until July 1, 1940, she had several divided courses of radiation (to the same areas as before), totaling 3,000 r. units. Her blood picture was maintained at a level of 70 per cent Hg with 3.8 million red blood cells by three 500 c.c. citrate transfusions during that period as well as by iron therapy orally. Suddenly, during the end of July she began to experience periods of pyrexia accompanied by a severe anemia and sudden enlargements of the cervical, inguinal, and axillary nodes. She was readmitted to the Bronx Hospital (No. 113637) on Aug. 1, 1940. Despite two 500 c.c. transfusions and 700 r. units of radiation in divided doses; her temperature ranged between 101° and 103° F., of the septic type; hemoglobin fell to 48 per cent with 2.6 million red blood cells and her condition became poor. On August 10, she was transferred to the Presby-

## NONPUERPERAL INVERSION OF THE UTERUS

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IN THE present case there was no evidence of a recent pregnancy, the last child being delivered seven years previously. Neither were there any tumors or other masses that might have predisposed to its formation.

Mrs. F. O., aged 38 years, was received in the emergency room of the Bronx Hospital on July 18, 1940, at 5:30 P.M. She complained of vaginal bleeding in conjunction with sharp abdominal pains, intermittent in character, which had begun five hours earlier.

She had been seen at the gynecological clinic during the previous month because of vaginal bleeding. She had been told that she was three months' pregnant and was advised to have a Friedman test. She did not return to the clinic. It had been further learned though that, for a year prior to admission, she had been having metrorrhagia. During the past two weeks there was some slight abdominal enlargement and some fluid had been seeping from the vagina.

Her menstrual history was normal. She had had three children, the youngest was born seven years previously at Lincoln Hospital. There was no history of miscarriages or abortions in the interim.

Examination showed an obese adult, well developed and not in acute shock or distress. Her heart and lungs were normal. The abdomen was soft with no masses or tender areas; the liver and spleen were not palpable. Pelvic examination showed active bleeding; a corrugated mass was found to fill the upper part of the vagina. The provisional diagnosis was incomplete abortion, and the patient was taken to the operating room where she was prepared for the removal of the retained placenta.

When the vagina was exposed there was a sudden gush of a moderate amount of serosanguineous fluid and a purplish mass presented itself. This was thought to be the placenta. It was grasped with an ovum forceps and gently pulled upon, whereupon a small piece partially tore away from the mass. All manipulations were immediately discontinued and, with the patient under anesthesia a re-examination was begun. The mass was found to be purplish, edematous, and about the size of a large grapefruit. It extended upward in the form of a truncated cone, the base being wider than the apex and the cervical rim was palpated high in the vaginal vault. It was rough in contrast to the smooth feel of the vaginal mucosa. No evidence of polyps, pedunculated fibroids, or any products of conception were found. A diagnosis of inversion of the uterus then became evident and attempts were made at reposition. This proving unsuccessful, the vagina was then packed with iodoform gauze. Later attempts at reposition were again unsuccessful. The vagina was re-packed and the patient was prepared for immediate laparotomy.

The abdomen was entered through a suprapubic incision. On opening the peritoneum the diagnosis was confirmed. Both ovaries and part of the tubes were in the concavity of the inversion. The iodoform vaginal packing was removed and with the assistant's hand in the vagina, efforts were made to reduce the inversion, but without success. A complete hysterectomy was then performed and iodoform gauze was placed in the vagina before its closure was completed. A cigarette drain was then placed in the cul-de-sac and the abdomen closed in the usual manner.

The patient received a citrate blood transfusion, of 500 c.c. immediately after the operation. This was followed by a continuous intravenous infusion of 2,500 c.c. of glucose (5 per cent) in saline, within the next twenty-four hours. The blood

months' baby cried immediately and lived only for six hours in the Drinker respirator. Again, the puerperium was uncomplicated.

The patient continued well and returned to us on June 12, 1938, stating her last menstrual period was April 18, 1938. She was found to be pregnant. Her prenatal course was uncomplicated until Oct. 22, 1938, at which time she was given bed rest for slight elevation in blood pressure. On Oct. 29, 1938, she had a small amount of painless vaginal bleeding. The baby was lying transversely. She was hospitalized but the bleeding increased. Examination revealed a placenta previa and a transverse lie. A low modified cervical cesarean section was performed, the diagnosis was confirmed, and a dead baby of 6½ months' gestation was removed. Palpation of the uterine cavity revealed a developmental defect of the uterus. It was shaped like a bicornuate uterus with the larger horn on the right. This defect was not marked, but upon close scrutiny it made the uterus appear heart-shaped. A section of the endometrium was removed for biopsy because of its roughness. Biopsy showed masses of decidual cells with areas of necrosis. The patient's postpartum course was uneventful.

TABLE I

AUTHOR	NUMBER OF SUCCESSIVE PLACENTA PREVIA	SUSPECTED CAUSE
Binder <sup>2</sup>	2 placenta previa in 1 case	Not given
Mitchell <sup>3</sup>	2 placenta previa in 1 case	Not given (occurred in gravida vii)
Gilliat <sup>4</sup>	4 placenta previa in 1 case	Not given
Gilliat (Case of Fitzpatrick)	5 placenta previa in 1 case	Not given (occurred in fifth through ninth pregnancies)
Gilliat (Case of Hedback)	2 placenta previa in 1 case	Not given
Gilliat (Case of Rivett)	5 placenta previa in 1 case	Not given
MacCarthy <sup>5</sup>	4 placenta previa in 1 case	Not given (occurred in tenth through thirteenth pregnancies)
Deutschman <sup>6</sup>	2 placenta previa in 1 case	Exophthalmic goiter and uterine fibroids

A review of the literature reveals 8 cases of placenta previa occurring in successive pregnancies. To these we add our case with three successive placenta previas. In a case reported by Otero y Gama, M. (1927): there were two placenta previas but not successively (in the patient's third and fifth pregnancies). Table I gives the author, the number of successive placenta previas occurring in each patient or case, and cause suspected.

## REFERENCES

- (1) Solomon, B., and Canter, H. E.: Surg., Gynec. & Obst. 54: 790, 1932. (2) Binder, J.: AM. J. OBST. & GYNEC. 28: 92, 1934. (3) Mitchell, R.: Canad. M. A. J. 24: 265, 1931. (4) Gilliat, W.: Proc. Roy. Soc. Med. (Sect. Obst. & Gynaec.), 17: 3, 1923. (5) MacCarthy, T.: Brit. M. J. 1: 95, 1928. Deutschman, D.: M. J. & Rec. 127: 555, 1928. (7) Otero y Gama, M.: Rev. Asoc. med. mexi. 6: 11, 1927.



in width surrounding a deep dimpling into which both tubes and ovaries had been drawn. The ovaries showed no evidence of recent corpora lutea.

Microscopically, sections showed myometrium and a small amount of endometrium characterized by diffuse edema and congestion. The outstanding feature of this tissue was the presence of widely dilated sinuses, many of which were intensely congested, some seemingly filled with blood and edematous fluid, giving the picture of an early infarction.

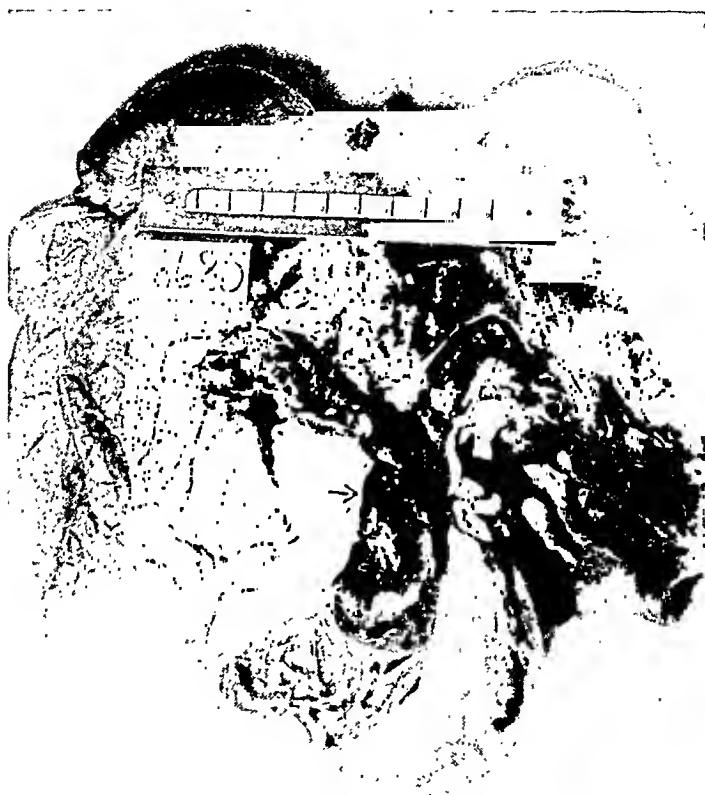


Fig. 2.—Necropsy specimen exhibiting elongated, massive, twisted thrombus, extending into both pulmonary branches from right ventricle (Accession No. 18685).

*Autopsy.*—Both the small and large intestines showed a generalized moderate degree of distention. There was about 1,500 c.c. of cloudy yellow fluid in the pelvis. The operative closure of the hysterectomy was complete with the sutures intact. There was no pus in the pelvis and no communication of the pelvic cavity with that of the vagina. In the great vessels of the heart, there was a massive embolus which extended from the right ventricle into the pulmonary artery, into the right and left branches, and into both lungs. The embolus was 1 by 1½ cm. wide and approximately 12 in. long, being all curled up. There was a post-mortem clot in the right ventricle separate and distinct from the embolus.

#### COMMENT

A case of uterine inversion is presented where the symptoms were of one year's duration and not related to pregnancy or the puerperal state. The etiologic factor was unknown. No pedunculated fibroids or other intrauterine masses were found. The sudden death was due to a large pulmonary embolus.

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pressure at the time of operation was 88/44. One cubic centimeter of cortate was given for shock and  $\frac{1}{4}$  gr. of morphine sulphate for sedation. One hour after operation the blood pressure was 104/64, pulse 80, and temperature 100° F. On the following day, the patient was fairly comfortable, the abdomen slightly distended, and she vomited once. Prostigmin 1:2,000 had been given every four hours. She voided spontaneously after the operation. When the wound was dressed, the gauze was found to be saturated with serosanguineous fluid. On the second postoperative day the patient did not vomit, but the distention persisted, and it was necessary to institute a Wangensteen drainage. Her temperature rose steadily, reaching 103.6° F. on the third and 104.6° F. on the fourth day, although the patient stated that she was comfortable. The distention however increased. On the fifth day, at 9:50 in the morning, while the patient's bed was being changed, she complained of a sudden pain in the right side of her head. She turned over and stopped breathing. Stimulation was of no avail.



Fig. 1.—Inversion of the uterus with both ovaries and tubes (shown at bottom of photograph) being drawn into the inverted area (Accession No. 18666).

On the day of admission (July 18) her urine was negative, but on the next day showed albumin 2-plus with many red blood cells. On the twentieth the albumin was 1-plus, and there were numerous red blood cells. Her blood test on the eighteenth showed Hb, 88 per cent; white blood count, 15,500; polymorphonuclears, 79 per cent; and lymphocytes, 18 per cent. Four days later the white blood count dropped to 11,900, polymorphonuclears 86 per cent, and lymphocytes 6 per cent.

*Gross Pathology* (Dr. Felsen).—The specimen is an inverted uterus 17 by 9 by 7 cm. The vaginal portion consisted externally of dark hemorrhagic soft tissue, the most dependent portion of which was markedly lacerated so that portions of tissue hung from it on a pedicle. The abdominal portion consisted of a serosal area 5 cm.

but cannot account for the development of the tumor in more protected regions as the esophagus, larynx, and retromammary space. Robert Meyer<sup>3</sup> reached the conclusion that this neoplasm results from an abnormal differentiation of the mesenchyme cells which ordinarily give rise to connective tissue. In some instances trauma may be the causative factor which starts this abnormal differentiation.

In the normal development of voluntary muscle cells, the individual cell passes from a syncytial stage to a myoblastic stage and thence to a myofibrillar stage. Godlewski, quoted by Klemperer,<sup>2</sup> describes the characteristic features of the myoblastic stage as consisting of large polygonal cells in ribbonlike masses with conspicuous cytoplasm free of fat. The description is essentially that represented in Figs. 1 and 2 of the mass removed from the labium majus.



Fig. 1.

Fig. 1.—Low power.  $\times 150$ . Van Gieson stain. Typical field showing interlacing collagen bundles (dark fibers) and groups of large polyhedral pale cells with granular cytoplasm.



Fig. 2.

Fig. 2.—High power.  $\times 350$ . Van Gieson stain. Detail of field in Fig. 1 showing structural characteristics of nuclei and cytoplasm of the myoblasts.

Although the myoblastomas are composed of immature muscle cells, they are innocent neoplasms and should be treated with conservatism. They grow slowly, are well encapsulated, do not metastasize, and do not recur. Sarcomatous changes have been noted in rare instances.<sup>6-8</sup> Macroscopically the tumor resembles a fibroma or fibromyoma, but these can be differentiated readily by the histologic picture.

#### SUMMARY

An unusual tumor of the labium majus having the appearance of a myoblastoma is described. The mass was removed and has not recurred in six months of observation. Other cases reported since 1926 indicate the benign nature of the tumor.

#### REFERENCES

- (1) Abrikossoff, A.: Virehow's Arch. f. Path. Anat. 260: 215, 1926.
- (2) Klemperer, P.: Am. J. Cancer 20: 324, 1934.
- (3) Meyer, R.: Ztschr. f. Geburtsh. u. Gynäk. 104: 367, 1933.
- (4) Száthmáry, Z. V.: Ztschr. f. Geburtsh. u. Gynäk. 114: 371, 1937.
- (5) Gray, S. H., and Gruenfeld, G. E.: Am. J. Cancer 30: 699, 1937.
- (6) Sjögren, H.: Arch. f. Ophth. 134: 333, 1935.
- (7) Loi, L.: Arch. ital. di med. sper. 3: 343, 1938.
- (8) Cioni, C.: Ibid. 7: 484, 1936.

## MYOBLASTOMA OF LABIUM MAJUS

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**M**YOBLASTOMA was first described by Abrikossoff<sup>1</sup> in 1926. Since then about 100 cases are on record. In the series reported by Klemperer,<sup>2</sup> the sites of predilection are beneath the skin and mucous membranes of the tongue, maxilla, and vocal cords. Isolated instances of involvement of the breast, lip, calf of leg, and esophagus have been reported. Száthmary<sup>4</sup> removed one from the labium minus during a vaginal plastic operation. The authors wish to add to the growing collection of myoblastomas one that developed in the labium majus.

E. S. (Case 100-642), female, white, age 39 years, was admitted to Lebanon Hospital on the Gynecological Service of Dr. A. J. Rongy on Nov. 27, 1940, complaining of a small lump in the right labium majus. She first discovered the presence of this mass three years ago due to itching of the overlying skin. During this period the tumor has grown slightly.

The previous medical and surgical history was negative. Venereal diseases were denied. Menstruation began at 13 years, recurred regularly every twenty-eight days and lasted four days. The last menstrual period started Nov. 16, 1940. She had been delivered of two children, the first by forceps. She had one spontaneous abortion.

Physical examination revealed a well-preserved adult female not acutely ill and with no defects except in the region of the vulva. A hard, freely movable, non-tender nodule about 2.5 cm. in diameter could be palpated in the anterior portion of the right labium majus immediately beneath the skin. There were no ulcerations present. No similar nodules could be found elsewhere in the body.

The blood Wassermann was negative. Hemoglobin was 74 per cent; red cells, 4,000,000; white blood cells, 7,000; polymorphonuclears, 63 per cent; lymphocytes, 33 per cent; mononuclears, 4 per cent. The urine was normal.

The clinical diagnosis was fibroma or sebaceous cyst of the labium majus.

The following day the tumor was enucleated under local anesthesia. The patient was discharged on Nov. 29, 1940. There has been no recurrence of the tumor up to the present time.

The pathologic report of Dr. Joseph C. Ehrlich follows: "Specimen 5956. Received a mass of tissue about the size of an olive. It is very firm and elastic and has the consistency of a hard rubber ball. The external surface is well delineated. It cuts with difficulty because of its marked density. On section it appears like dense connective tissue. Microscopic sections reveal this tissue to be composed of interlacing bands of broad collagen fibers between which are variously shaped groups, nests and strands of large pale cells. Some of these cells are polyhedral in form; others are band shaped. The nuclei are small and generally pale and centrally placed. The cytoplasm is very pale or invisible and contains fine granular material. There is a superficial resemblance to xanthoma cells. However, fat stains are negative. Some of the band forms contain several nuclei. The admixture of groups of pale cells and interlacing collagen fibers is uniform and extends from the connective tissue capsule to the vulvar skin surface. The histologic picture is characteristic of myoblastoma."

The appearance of a muscle tumor beneath the skin and mucous membranes, where there is normally no voluntary muscle, has given rise to much speculation as to its origin. Abrikossoff regards the tumor as the result of faulty excessive regeneration subsequent to injury. Gray and Gruenfeld<sup>5</sup> maintain that the cells are muscle fibers undergoing necrobiotic changes rather than a neoplastic alteration. These theories may explain the origin of the growth in sites vulnerable to injury

tempted. Only very small amounts of placental tissue could be removed and no line of cleavage could be established. At this time parenteral fluids were administered and the patient received 500 c.c. of blood by transfusion. Inasmuch as uterine bleeding continued, manual removal was unsuccessfully tried forty-eight hours after the first attempt, and the diagnosis of placenta accreta was confirmed. Because of the continuing poor condition of the patient, hysterectomy was deferred until major surgical intervention should be warranted.

A septic course ensued, with a temperature of 104° F. on the fourth post-partum day, accompanied by chills. A copious amount of foul-smelling discharge was noted throughout her hospitalization. Because of the patient's generally poor condition, accentuated by a profound anemia which did not respond to blood transfusions and liver and iron therapy, a hysterectomy was at no time thought advisable. On the tenth post-partum day her temperature and pulse began to subside and on the twenty-first post-partum day her condition warranted dismissal from the hospital. She was seen at regular intervals at the out-patient clinic where hematopoietic therapy was continued. Ten weeks later, complaining of unmarked backache and constant pain in the left lower abdominal quadrant, she was again admitted to the hospital. Pelvic examination showed marked relaxation of the pelvic floor and a patulous external cervical os. The uterine corpus was forward and well involuted, with some induration and tenderness in the region of the left adnexa.

A panhysterectomy, bilateral salpingectomy, and unilateral oophorectomy were performed through a midline incision by Dr. E. C. Sage. The uterus was found to be soft, of approximately normal size, and adnexal organs were normal in appearance. Upon gross examination, the cut section of the uterine corpus showed a "quite ragged endometrium but without evidence of inflammatory reaction or material which can be recognized as placental tissue."

The microscopic section, as reported by Dr. P. Tollman, showed "the endometrial surface to be covered with rather ragged masses of granulating tissue in which there are roughly circumscribed masses of very necrotic tissue which are quite uniformly pink staining. In some places this is definitely papillary in type. In a few places large and rather irregular cells remain about the border of these, which are interpreted as patchily degenerating decidual cells. This necrotic mass strikingly resembles chorionic villi undergoing degeneration. The surrounding tissue is moderately to heavily infiltrated with lymphocytes. There is an unusual amount of rather loose fibrous tissue scattered through the wall and the larger arteries show a prominent endarteritis of the type associated with atrophy of tissue." Examination of a second section was similar except for the absence of chorionic villi.

When last seen, this patient was well and had no pelvic complaints.

#### DISCUSSION

Careful search of the literature shows that all outstanding authorities without exception recommend immediate supravaginal hysterectomy as the treatment of choice after diagnosis of placenta accreta has been established. This procedure is augmented by transfusion both before and after surgery. Meyer and Ashworth's<sup>1</sup> tabulations show a mortality of 58 per cent in manual extraction or curettage; 36.4 per cent in partial manual extraction and vaginal hysterectomy; 18.9 per cent in partial manual extraction and supravaginal hysterectomy; and no mortality in supravaginal hysterectomy with no attempt at extraction.

From the mortality standpoint, this latter procedure would seem to be the method of choice. However, if no attempt at extraction is made, diagnosis is impossible because the inability to establish a line of cleavage is what differentiates placenta accreta from the simple adherent placenta. It would seem extremely radical to perform a supravaginal hysterectomy on each and every retained placenta that is not bleeding

## PLACENTA ACCRETA

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ONLY 118 authentic cases of placenta accreta have been reported, according to Meyer and Ashworth's<sup>1</sup> tabulation in 1940, after careful perusal of the literature. The incidence of this pathologic condition varies greatly: Tiemeyer<sup>2</sup> reports it on two occasions, a ratio of 1 in 2,156 cases; Lawson and Oginz<sup>3</sup> report that Polak in 34 years' experience encountered but one case in every 6,000, and that Hirst found this anomaly only once in 40,000 deliveries.

The etiology of placenta accreta is found in the partial or complete absence of the decidua basalis, allowing the villi to burrow directly into the uterine musculature, which in turn causes the placenta to be retained within the uterine cavity. Any condition producing a primary atrophy of the endometrium may be a factor in the causation of an accreta. The etiologic factors of prime importance are: previous manual removal of the placenta, too thorough curettage, endometritis, submucous myomas, previous cesarean section, and possibly dysharmonism.

The chief symptom is more or less brisk bleeding when delivery of the placenta is attempted. The diagnosis is made after an attempt at manual removal has failed to establish a cleavage plane between the placenta and the uterine musculature, thus showing retention of the placenta within the uterine cavity.

Thorough search of the literature has shown the agreement of all authorities that immediate hysterectomy is imperative as soon as a diagnosis of placenta accreta has been made. The following report is therefore presented, since treatment in this case varied so greatly from the orthodox management of this anomaly.

### CASE REPORT

Mrs. R. B., aged 44 years, white, gravida xii, para xi, had no history of major illnesses. All the patient's children had been born at home and labors were easy and uncomplicated except the pregnancy just prior to the present one which had terminated at eight months in a premature stillbirth. The cause of the prematurity was unknown.

The present pregnancy was uneventful during the first two trimesters; the expected date was estimated as Sept. 22, 1932. On July 24, 1932, the amniotic sac ruptured spontaneously, and thirty-six hours later the patient was delivered normally of a live premature child at her home with the family physician in attendance.

Two hours later, after failure of the placenta to deliver and because of profuse bleeding per vaginam, the patient was sent to the University Hospital. She complained of nausea and a great deal of abdominal pain. Shock was combated by hypodermic injections of morphine and application of external heat. Later the same day, because the bleeding continued, manual removal of the placenta was at-

# Society Transactions

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## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF MARCH 21, 1941*

The following papers were presented:

**The Role of Cesarean Section in the Toxemias of Pregnancy.** Drs. Herman A. Strauss and Leah Fisher (by invitation). (For original article, see page 440.)

**A Method for Reducing the Size of the Uterus in Vaginal Hysterectomy.** Dr. A. F. Lash. (For original article, see page 452.)

**The Shortening of Labor With Syntropan.** Dr. John E. Stoll (by invitation). (For original article, see page 473.)

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## BROOKLYN GYNECOLOGICAL SOCIETY

*MEETING OF MAY 2, 1941*

The following papers were presented, dealing with the Causes of Puerperal Mortality in Brooklyn.

**Anesthesia.** Dr. Henry S. Acken, Jr.

**Cardiac Disease.** Dr. Thomas R. Turino.

**Infection.** Dr. Joseph E. Hall.

**Hemorrhage.** Dr. Alexander H. Rosenthal.

**Cesarean Section.** Dr. James L. O'Leary.

**Toxemia.** Dr. Frank P. Light.

**Summary.** Dr. Charles A. Gordon.

and that has not been expelled within two hours' time, as some writers have suggested. Stander<sup>4</sup> warns that if a prompt hysterectomy is not done directly following the diagnosis, death from hemorrhage usually follows.

In the case presented after the diagnosis of accreta had been made, and measures to combat the acute anemia and shock resorted to, at no time during the immediate puerperium was the patient's condition sufficiently good to warrant supravaginal hysterectomy. The writer feels confident that surgical intervention would have been fatal.

At the time of the patient's readmittance to the hospital, because of her previous condition, removal of the uterus was thought advisable. But postoperative examination of the uterine corpus and the pathologic report showed that very likely no further pathologic condition of the placenta needed to be feared.

This case is reported to emphasize the successful outcome of unorthodox treatment in the immediate puerperium of placenta accreta.

#### REFERENCES

- (1) *Meyer and Ashworth*: Virginia M. Monthly 67: 36, 1940. (2) *Tiemeyer, A. C.*: South. M. J. 31: 608, 1938. (3) *Lawson and Oginz*: Am. J. Surg. 41: 70, 1938. (4) *Williams Obstetrics (Stander)*, ed. 8, New York, D. Appleton-Century Co.
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Campbell, Meredith F.: Vulvar Fusion, J. A. M. A. 115: 513, 1940.

Fused vulva designates the condition characterized by an embryonal midline sealing together of the labia minora. As a rule an unfused area is left well forward and through this orifice the child urinates. This condition is either congenital, or acquired through inflammatory changes. The most rational explanation for the embryologic type is fusion in the midline of the labial folds, similar to that which the two scrotal folds undergo in the male, but the fusion usually lacks the density of scrotal fusion. Acquired vulvar fusion is said to follow local inflammation consequent to acute infectious diseases such as cholera, smallpox, diphtheria, scarlet fever, pneumonia, typhoid, and typhus.

The clitoris is likely to be completely covered, and the entire area appears to be all perineum. In cases of complete fusion the expulsion of urine can take place only through a congenital vaginorectal fistula or a urethrovaginorectal fistula. In other words, complete vulvar fusion in the absence of an adequate urinary exit means an unviable fetus or child. The line of fusion is well exterior to the hymenal structure. The condition is confused chiefly with hermaphroditism and pseudo-hermaphroditism. Hematocolpos, hematometra, and pyuria may complete the condition. Treatment consists in separation of the vulva by an incision in the cleavage line or midline of fusion.

WILLIAM BERMAN.



23 with moderate or much vernix. The author feels, therefore, that vernix is abnormal and is one of the signs of vitamin A deficiency. The incidence of vernix can be influenced by the administration of vitamin A to the mother. Vitamin A is not only an antikeratinizing factor, but it is also necessary for the keratinization of the adult epidermis, and it is logical to assume that it is, therefore, necessary for fetal epidermis. Vernix caseosa is composed of the same elements as vitamin A dermatoses in the adult, and the author concludes that careful observation of a larger series of pregnant women and newborn will soon reveal that vernix is a manifestation of vitamin A deficiency.

WILLIAM BERMAN.

Ford, Norma, Ross, Mary A., and Brown, Alan: Primogeniture as an Etiologic Factor in Pyloric Stenosis, *Am. J. Dis. Child.* 61: 747, 1941.

An investigation of the order of birth in 405 cases of pyloric stenosis (seen in the Hospital for Sick Children in Toronto) showed that in 50.1 per cent the patient was a first-born child. By comparison less than 41.2 per cent of the children in Toronto were first born. This difference of 10.6 per cent is shown by the writers to be statistically significant, and the importance of primogeniture as an etiologic factor in pyloric stenosis is indicated.

HUGO EHRENFEST.

Penrose, L. S.: Maternal Age, Order of Birth and Developmental Abnormalities, *J. Mental Sc.* 85: 1141, 1939.

According to Penrose a positive association is demonstrable between maternal age and the incidence of mongolian imbecility, gross malformation of the nervous system, and central placenta previa. The independent effect of birth order is not easy to demonstrate conclusively. Primogeniture, however, is likely to be a significant factor in determining the incidence of gross malformation of the nervous system and of congenital pyloric stenosis. The study of maternal age and birth order usefully precedes the investigation of the genetical backgrounds of these conditions. The underlying cause of congenital pyloric stenosis seems to be a recessive diathesis. Mongolism and some other malformations may have their origin in chromosome anomalies.

J. P. GREENHILL.

Hellman, L. M., and Shettles, Landrum B.: Factors Influencing Plasma Prothrombin in the New Born Infant, *Bull. Johns Hopkins Hosp.* 65: 138, 1939.

The average plasma prothrombin level in 18 mothers and 19 full-term newborn infants was 102.5 and 22.2 units, respectively.

The average plasma prothrombin level in 8 mothers and 9 premature infants was 126.9 and 8.3 units, respectively.

Preliminary studies indicate that these extremely low infant prothrombin levels can be raised by feeding vitamin K to the mother prior to delivery, or directly to the infant after birth.

C. O. MALAND.

Nygaard, K. K.: Prophylactic and Curative Effect of Vitamin K in Hemorrhagic Disease of the Newborn (Hypothrombinemia Hemorrhagica Neonatorum), *Acta obst. et gynec. Scand.* 19: 361, 1939.

A preliminary report is presented dealing with observations on the changes in the coagulability of the blood in 54 newborn infants. The author found that the prothrombin time appears to be normal at the time of birth. From the second half of the first day to the sixth day of life, a physiologic, transitory hypothrombinemia is present. In the majority of cases of hemorrhagic disease of the newborn, the onset of hemorrhage occurs during this period. Cases in this group presenting

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### The Newborn Infant

Sontag, Lester Warren: Effect of Fetal Activity on the Nutritional State of the Infant at Birth, *Am. J. Dis. Child.* 60: 621, 1940.

Available evidence indicates that the system of placental transmission may limit the amount of glycogen and fatty acids available for fetal needs.

Active and frequent fetal movements require the consumption of considerable amounts of energy-producing foods which otherwise might be stored as fetal fat. Excessive fetal activity, therefore, may be responsible for considerable underweight at birth. Many factors influence fetal activity, among them sounds, maternal fatigue, or emotion.

The environment of the infant during its intrauterine life is a subject worthy of a great deal more study than is customarily bestowed.

HUGO EHRENFEST.

Gray, H., and Eder, H. L.: Big Babies and Their After-History, *Am. J. Dis. Child.* 61: 717, 1941.

The frequency of births of babies weighing over 4,000 gr. has been reported as varying all the way from 1 per cent in Tokyo to 15 per cent in Esthonia. From the study of 12 such babies, the writers conclude that babies big at birth tend to continue to weigh more than average at least during the first two years of life.

HUGO EHRENFEST.

Straumfjord, Jon V.: Vernix Caseosa; a Manifestation of Vitamin A Deficiency, *West. J. Surg.* 48: 341, 1940.

The author has observed patients who develop follicular keratosis during pregnancy. He notes that some mothers with this condition give birth to babies with vernix. Some doubt is raised concerning the function of the vernix. Kiupers became interested in the relationship of vitamin A to vernix. He found no noteworthy difference either in the vitamin A content of the vernices or in the incidence of the birth of babies without vernix when mothers are divided according to different economic levels.

In this report the author has attempted to influence the incidence of vernix by oral administration of vitamin A to pregnant women. Fifty thousand to 100,000 units of vitamin A were given to 25 women through six months or more of pregnancy. Twenty-one had babies with little or no vernix and 4 with moderate or much vernix. Twenty-nine women received some additional vitamin A, but much less than the women of the first group. In this group, 14 babies had little or no vernix and 15 babies had moderate or much vernix. Thirty-one women had no additional vitamin A. Eight babies in this group were born with little or no vernix and

levels are not significantly elevated in infants with retinal hemorrhage, born of mothers treated during labor. The administration of vitamin K to mothers prior to the onset of labor almost entirely eliminates retinal hemorrhage in their infants.

C. O. MALAND.

**Thoms, Herbert:** Observations on the Roentgenological Evidence of Fetal Death, Surg., Gynec. & Obst. 71: 169, 1940.

At the present time there is no definite roentgenologic procedure which in all cases can be considered pathognomonic of fetal death in utero within the first week after this event has taken place. Recognizing the fact that brain collapse is an early change, our attention should be drawn to the consideration of this change in viewing roentgenograms. It may be that serial roentgenograms taken at twenty-four-hour intervals, with particular study of the fontanels and sutures, may give suggestive information concerning brain collapse, as in the case cited.

WILLIAM C. HENSKE.

**Pehu and Lefebvre des Noettes:** Pneumothorax in the Newborn, Rev. franç. de pédiat. 15: 393, 1939-40.

Among the causes of neonatal pneumothorax the authors list obstetric trauma; artificial stimulation of respiration; brain lesions not due to natal traumatism, such as intracranial hemorrhages; obstructions in the trachea, such as congenital goiter and hypertrophy of the thymus; infectious disease complications, such as lobar pneumonia; accidents caused by hypodermic puncture; bronchial and cardiac malformations, and a variety of causes of undetermined origin involving fundamentally rupture of the superficial alveoli of the lungs. Pulmonary tuberculosis may be eliminated as a causative agent. Three types of neonatal pneumothorax are distinguished (partial, total, high tension) and their typical roentgenographic features are indicated. Dyspnea and cyanosis, characteristic signs of pneumothorax of the newborn, need to be diagnostically differentiated from a pathologic condition, such as normal neonatal cyanosis, those occurring in cardiovascular malformations, and from tracheal thymus pressure, bronchial or bronchopulmonary air cysts, pulmonary atelectasis and bronchopneumonia. In all of these, clinical and roentgenoscopic observations combine to disclose the real facts. Prognosis is favorable in pneumothorax of traumatic origin and in congenital bronchial malformation in which no pathologic signs manifest themselves. In high tension, pneumothorax prognosis is likewise good, provided pleural punctures succeed in preventing recurrence of air infiltration. The authors point out that the mechanism of the physiologic function of breathing when the infant first establishes independent respiration is still imperfectly understood, no elucidating roentgenograms yet existing. These mechanical factors occupy an important place in the pathogenesis of infant pneumothorax.

J. P. GREENHILL.

**Paterson, J. C., and Farr, J. T.:** Pulmonary Collapse as a Cause of Neonatal Death, Canad. M. A. J. 41: 31, 1939.

From a study at necropsy of 13 stillborn infants and 12 infants who died during the neonatal period, evidence was obtained to support the belief that there is a tidal flow of amniotic fluid through the bronchial tree and pulmonary alveoli due to intrauterine respiratory movements. It is suggested that the lungs of newborn human infants contain potentially obstructing masses derived from the solid elements of amniotic fluid which may become actively obstructive if the respiratory activity is inadequate. Pulmonary collapse in the newborn appears to result from the absorption of the alveolar air entrapped distal to a point of obstruction by amniotic fluid debris.

evidence of hemorrhage, exhibit a more marked hypotherbinemia than is normally characteristic for this stage of life. This pathologic condition has been termed hypotherbinemia hemorrhagica neonatorum.

The development of transitory hypotherbinemia appears to be successfully prevented by the administration of vitamin K right after delivery. This may eventually lead to effective prophylaxis of hypotherbinemia hemorrhagica neonatorum. Vitamin K administered to three babies with this type of hemorrhage exhibited a therapeutic effect equal to that of blood transfusion.

J. P. GREENHILL.

MacPherson, A. I. S., McCallum, E., and Haultain, W. F. T.: Effect of Intrapartum and Neonatal Administration of Synthetic Vitamin K Analogues on the Newborn, *Brit. M. J.* 1: 4141, 1940.

Cord blood prothrombin index in 32 cases was found to vary widely, to be about 75 per cent of that of maternal blood, and to be unrelated to length of labor or type of delivery. Two of 5 toxemias showed marked maternal prothrombin deficiency and the cord blood showed a 15 to 20 per cent lower prothrombin index.

Prothrombin index was found to vary extremely in different individuals and in the same individuals from day to day. A decrease in prothrombin index was often demonstrated within twenty-four hours, reaching the lower level in thirty-six to eighty-four hours, then rising sharply about the fifth post-partum day to about 75 per cent. The extent of the decrease was influenced by (1) prothrombin index of the cord blood, (2) abnormal deliveries, and (3) maternal toxemia. When given a vitamin K analogue, 2 methyl-1:4 naphthoquinone in the first twenty-four hours, the prothrombin index was raised to 80 or 90 per cent and stabilized at this level for three to four days. The effect was noticeable within several hours. Administration to babies during the first twenty-four hours and to mothers during or immediately before labor, preferably twelve to four hours before delivery, gave similar results.

Association of unduly low prothrombin index, generally where there has been maternal toxemia or difficult labor, and prompt relief of cerebral symptoms on the administration of a vitamin K analogue suggests the value of further therapeutic trial.

FRED L. ADAIR AND JOHN R. KIGHT.

Fiechter, N.: Hypoprothrombinemia and Hemorrhagic Diathesis of the Newborn and Its Relation to Vitamin K, *Monatschr. f. Geburtsh. u. Gynäk.* 111: 1, 1940.

By means of Quick's method, Fiechter was able to discover in the first week of life, a physiologic delay in the clotting time which was due to a deficiency of prothrombin. This normal transient disturbance in clotting time exists, to a slight degree, at the moment of birth and reaches its maximum between the third and fifth days of life. By means of vitamin K, the delay in clotting time of the newborn can be prevented. A similar effect can be produced by giving vitamin K to the mother sometime before labor. Hemorrhagic disease of the newborn also produced prolongation in the clotting time which coincides with the physiologic maximum between the third and fifth days. This prolongation in clotting time can be immediately reduced by vitamin K which at the same time stops bleeding. In the author's cases of melena neonatorum, vitamin K has replaced blood transfusion. In cases of intense jaundice, there was also a delay in clotting time. This, too, can be corrected by vitamin K.

J. P. GREENHILL.

Maumee, A. E., Hellman, L. M., and Shettles, L. B.: The Effect of Antenatal Administration of Vitamin K on the Incidence of Retinal Hemorrhage in the Newborn, *Bull. Johns Hopkins Hosp.* 67: 158, 1941.

Infants with retinal hemorrhage show lower prothrombin levels than normal infants. The incidence of retinal hemorrhage in the newborn can be slightly reduced through the administration of vitamin K to mothers during labor. The prothrombin

A case in which the face was the presenting part at the onset of labor and probably before, is described. The child was carefully studied and no lesion of the nervous system was found. By the use of simple orthopedic appliances the opisthotonus was gradually overcome, after about four months.

The author suggests the wisdom of overcoming the dearth of information in the literature dealing with this subject by carefully studying and reporting such material as it comes to hand.

J. L. McKELVEY.

Chapple, Charles C., and Davidson, Douglas T.: *A Study of the Relationship Between Fetal Position and Certain Congenital Deformities*, J. Pediat. 18: 483, 1941.

It is generally admitted that uterine wall pressure can affect the fetus in various ways and may play a role in the causation of certain congenital deformities. In this interesting and profusely illustrated contribution, the authors convincingly show that in some instances it is an abnormal fetal presentation which results in abnormal pressure leading to the specific skeletal anomaly evident at birth or soon afterwards. In this respect the hip is the most commonly affected joint.

It is emphasized by the writers that it is important to determine the "position of comfort" as a routine part of the examination of the newborn infant, both as a means of anticipation and prevention of bone and joint abnormalities and as an aid to the interpretation of existing deformities.

HUGO EHRENFEST.

Bruens, Egon: *Thoughts About the Use of Sulfanilamide During Pregnancy*, München. med. Wehnsehr. 87: 1213, 1940.

Bruens had occasion to treat newborn children for gonorrhea neonatorum with sulfanilamide (albuacid) and other similar preparations, and although these products might be well tolerated by the adult this is not true for the newborn infant. The younger the infant the sooner do toxic signs and symptoms appear. In view of this observation he suggests clinical and experimental studies be made on possible toxic effects to the unborn child when sulfanilamide is administered to the expectant mother. Present conditions and circumstances make it impossible for him to study this problem.

C. E. PROSHEK.

Von Pallos, Karl: *Two Cases of Sacral Teratoma*, Ztschr. f. Geburtsh. u. Gynäk. 121: 421, 1940.

Two characteristic cases of sacral teratoma in the newborn are described in detail. One of these tumors was made up of a mixture of tissue representing all three germ layers. The second showed fairly advanced development of organs, including a rudimentary extremity.

About two-thirds of these fetuses may be expected to deliver spontaneously and the rest will be handled by traction or destructive operations. A third of the babies will be born dead and a large number of the rest will not survive the first year. Living children should be promptly treated surgically because of the danger of necrosis and infection of the tumor mass.

J. L. McKELVEY.

Brander, T.: *Concerning the Os Fonticuli Frontalis and Its Clinical Significance*, Acta obst. et gynec. Scandinav. 20: 372, 1940.

The literature concerning os fonticuli frontalis (bone in the anterior fontanel) is based chiefly on studies by anatomists. Clinical observations were recorded in only 3 cases. One of these babies died during labor, the second died at twenty-five days, and the third was presumably normal at five weeks of age. In cases of

Underlying causes of inefficient respiratory movements immediately after birth and during the neonatal period are prematurity, respiratory depression by excessive antepartum analgesia, prolonged anesthesia, and pressure from cerebral hemorrhage. Suggested treatment includes prophylaxis against these underlying causes with routine treatment directed at aiding removal of amniotic fluid debris from the lungs by postural drainage, bronchial and tracheal catheterization under laryngoscopic control, and increasing the depth of respiration by use of a respirator. Oxygen should be administered through a nasal catheter rather than by the use of the mask type of inhalations which the authors believe may result in absorption collapse of the lungs due to the absence of inert gases in pure oxygen or carbon dioxide-oxygen mixtures.

CARL P. HUBER.

Fisher, John H.: Spontaneous Pulmonic Interstitial and Mediastinal Emphysema in an Infant, *Canad. M. A. J.* 44: 27, 1941.

Interstitial emphysema of the lungs and mediastinum probably occurs more frequently than is at present recognized although it seldom produces a fatal outcome. In this paper the author describes an infant, born spontaneously at term, who died of increasing respiratory embarrassment within five and three-fourths hours. Respirations were normal at birth, with good color. At necropsy the left lung was largely atelectatic and small in volume. There were some interstitial emphysema and a few subpleural emphysematous blebs. These findings were more marked on the right side. Both lungs showed an accumulation of gas bubbles in the perivascular sheaths of the pulmonary vessels which was sufficient to significantly compress the vessels. It was considered that the emphysema resulted from an overinflation of the alveoli producing multiple ruptures and an escape of air into the perivascular sheaths. It is probable that this resulted in this case from a failure of normal expansion of the left lung with compensatory overinflation of the right lung. Fixation of the lungs in the distended position is important in studying the distribution of the escaped air and its relation to the lung structures.

CARL P. HUBER.

Kastendieck: Etiology of Congenital Torticollis, *Zentralbl. f. Gynäk.* 63: 727, 1939.

Congenital torticollis or wryneck is an intra-uterine deformity and is not caused by the trauma of labor. It occurs chiefly in breech presentations but may be found in cases which present by the head. There is a tendency for some women to have repeated breech presentations, and because of this there is an indirect hereditary tendency to the development of torticollis.

J. P. GREENHILL.

Ottow, B.: Prolonged Opisthotonus in the Newborn Following Delivery in Face Presentation, *Ztschr. f. Geburtsh. u. Gynäk.* 121: 39, 1940.

The occurrence of torticollis and opisthotonus following breech delivery is discussed. The known familial tendency in the former is questioned in the light of the somewhat similar circumstances seen in opisthotonus which seems to have no familial relation.

The cause of the opisthotonus which occurs occasionally when the breech or the face has persisted as the presenting part is unknown. The various theories are discussed. There may be mild and clinically undetectable abnormalities of the upper cervical vertebrae. Dolichocephalus may play a part. It is not clear whether the extended head in the breech and when the face persists as the presenting part is caused by, or the result of, the opisthotonus seen after delivery. The author leans toward the view that there is some other cause for the extension of the head in opisthotonus and the flexion in torticollis with a resulting lack of normal muscle stretching and an interference with normal blood supply.

The subjects and speakers will be announced later. Dr. Robert L. DeNormandie is Chairman of the Committee on Public Meetings.

There will be moving picture exhibits, and it is planned to devote the first morning exclusively to registration and moving picture exhibitions. Dr. Robert D. Mussey is Chairman and Dr. M. E. Davis is Secretary of this committee.

The Committee on Scientific and Education Exhibits is headed by Dr. H. C. Hesselstine with Dr. Charles Galloway as Secretary. They are planning a larger and better exhibit than the excellent one of 1939.

The important Membership Committee is functioning under the leadership of Dr. Buford Hamilton, who has organized a Central Committee with representation of each of the five groups interested in the Congress. State membership committees are being formed in all the states so that all interested groups may be represented. There are also committees for special organizations. The Central Committee will map out the general plan for each state committee to follow. In the main, their function will be to inform the central office of the agencies and individuals in their states who should be interested in this Congress and to see that all these agencies and individuals have information relative to the meeting. These membership committees are the only liaison between the central office and their members and they should do all they can to act as coordinators between the central office and their groups. In the more populous states it may be wise to have county, city, or regional committees to function in a similar manner.

Dr. Joseph A. Baer is serving as Chairman of the Committee on Lay Publicity. The personnel of this group will be announced shortly. We are extremely fortunate in again securing the services of Mr. James C. Leary. He served us most enthusiastically and satisfactorily during the session of the First Congress. Dr. George W. Kosmak and his committee have charge of the professional publicity for the various sections and will welcome any assistance in the way of securing local publicity through avenues which reach the various professional groups. Dr. W. C. Danforth is Chairman of the Budget and Finance Committee and Dr. Goodrich C. Schaffner has appointed the following representatives to work with him on the Publication Committee: Dr. Ben Black, Ernestine Wiedenbach, Dr. Howard Taylor, Jr., and Dr. Reginald M. Atwater.

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### American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 3, 1942, at 2:00 P.M. Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

Applications for admission to Group B, Part I examinations must be on file in the Secretary's Office not later than October 1, 1941. Applications for Group A must be in the Secretary's Office by March 1, 1942.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Atlantic City, N. J., immediately prior to the 1942 meeting of the American Medical Association.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

os fonticuli frontalis, palpation may lead to a wrong diagnosis. Brander reports a case which he kept under observation for eight months. His case proves that the bone in the anterior fontanel may lead to dystocia. The child developed bilateral cephalhematomas and the mother had a rupture of the vagina. The baby had a remarkable increase in the circumference of its head at one month of age and premature cranial closure at two and one-half months.

J. P. GREENHILL.

Gustafson, Gerald W., and Garceau, George J.: Cerebral Spastic Paralysis, J. A. M. A. 116: 374, 1941.

The authors report 185 instances of cerebral spastic paralysis with a detailed study of the labor in these cases. They feel that apnea resulting from anesthesia and analgesia played little, if any, part in this series. There was an increased tendency to cerebral injury in infants of mothers having less than twelve hours of labor. The greatest number of cases were found in women having normal spontaneous deliveries. Five cases followed cesarean section. Thirty per cent of the babies were premature. It is concluded that proper management of labor constitutes the best prevention of cerebral spastic paralysis, and that prevention and treatment of premature labor is the greatest single factor in the prevention of cerebral injury. Posterior pituitary extract continues to contribute to the incidence of cerebral spastic paralysis.

WILLIAM BERMAN.

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## Items

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### The Second American Congress on Obstetrics and Gynecology

The arrangements for the Second American Congress on Obstetrics and Gynecology to be held in St. Louis, Mo., from April 6 to 10, 1942, are progressing according to schedule. The various committees have been formed and are ready to function. The general program of meetings has been set up and meeting rooms in the St. Louis Auditorium have been assigned.

Efforts have been made to gauge the attitude of various commercial exhibitors toward the Congress with gratifying results. Especially encouraging is the interest shown by those who were not exhibitors at the First Congress in Cleveland in 1939. The floor plans for the exhibit space are being drawn up under the advice of representatives of the Medical Exhibitors Association, and the program is being arranged so that the members attending the Congress will have plenty of time to spend at the various booths and exhibits. Dr. Philip Williams of Philadelphia is Chairman of the Committee in charge of the Commercial Exhibits, while the details are being handled by Karl S. Richardson, Business Manager, in the office of the Congress at 650 Rush Street in Chicago.

The Program Committee, with Dr. E. D. Plass as Chairman and Dr. William F. Mengert as Secretary, is working with the various subcommittee chairmen who are: Dr. Ralph A. Reis, Medical Section; Miss Georgia Hukill, Nursing Section; Dr. R. C. Buerki, Hospital Section; Dr. Edwin C. Daily, Public Health Section; Dr. Clare Folsome, Educators Section.

The personnel of these committees will be announced in our next issue. The Central Program Committee met on Saturday, June 21, and progress was made in forming the general plan of the program which will conform to the following ideas: The program contemplates meetings of individual sections, of combined sessions, and of general sessions. Round table or panel discussions will be held by those sections which desire them. There will be evening sessions for the laity as well as for the members. Probably two evenings will be assigned to each type of meeting.



socialism. When Bismarck became alarmed at the rapid progress of socialism, in the early eighties of the last century, and when he found that he could not stem the tide by coercion or suppression, he decided to throw a sop to the socialists in the form of sickness and accident insurance, together with old age pensions, all of which were adopted within the decade. When he submitted the bills to the Reichstag he said: "Do this without fearing either sacrifice or the cry of state socialism for I believe the socialists will then sound their bird cry in vain." He predicted that the sop would silence the socialistic clamor and stop its advance. He was a poor prophet. Socialism kept on growing in Germany and spread rapidly to the following countries: Austria, 1883; Hungary, 1891; Finland, 1895; Great Britain, 1897; Denmark, France and Italy, 1898; Spain, New Zealand, British Columbia, 1902; Russia and Belgium, 1903; State of Nuevo, Mexico, 1906; Transvaal, 1907; Alberta, Bulgaria, Newfoundland, and the U. S. A. (for federal employees), 1908; Quebec, 1909; Nova Scotia, Manitoba, 1910; Switzerland and Peru, 1911; Rumania, 1912, and 45 of the states of the United States, 1911 to 1918. Within thirty years the proposed so-called socialistic proposals literally swept the world. One cannot say that such a tide of opinion is only passing agitation, nor can such a mass movement be retarded by merely asserting that it is wrong. While extreme radicalism seldom forces its own program successfully, it often does succeed in liberalizing conservative thought, so much so, indeed, that what seemed radical yesterday, becomes only liberal today and tomorrow may be looked upon as conservative. Perhaps we as a profession can derive some profit by these lessons of history, which illustrate the influence of changing social attitudes upon the problems of community health.

The United States took the first step toward social health insurance when it was adopted for federal employees only. The next step came with the adoption of workmen's compensation laws by forty-five of the states. It is with some chagrin that we must admit that the medical profession had little voice in their formulation and enactment. Employers, labor leaders, and lawyers were its principal proponents due, it was accused, to the truculent attitude of the medical profession.

It is not my purpose to discuss the merit or lack of worth of the many plans and schemes proposed but rather to consider the philosophy or lack of philosophy of organized medicine in meeting the issues. Twenty years ago I became rather concerned about the apparent indifference of the profession toward what seemed very radical trends and expressed the fear that unless we familiarized ourselves with them so that we could take an intelligent part in the discussions and decisions of the problems, others would decide them without us and in a way that might be unfair to the public and to us. After two decades I have the same fear. Now, as then, I am apprehensive that we may not be sufficiently social-minded to cooperate with other groups in meeting the issues. Medicine certainly cannot attain its proper place in society by resisting all of the impacts of social change.

Twenty years ago it appeared that the next step would be health insurance, compulsory or voluntary. However, even after two decades, the debate continues, but there seems to be increasing doubt concerning

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## American Gynecological Society

Sixty-Sixth Annual Meeting, May 26, 27, and 28, 1941

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### ADDRESS OF THE PRESIDENT\*

JENNINGS CRAWFORD LITZENBERG, M.D., MINNEAPOLIS, MINN.

FOR the subject of my address I have chosen "Medicine in the Changing Social Order." History is the record of constant political, economic, scientific, and social change. When the forces of construction prevail, like human welfare, political liberty, scientific research, economic freedom, and preservation of public health, the social structure is strong. When the forces of destruction prevail, such as war, pestilence or tyranny, human liberty is curtailed, industry wanes, science languishes, human health is in jeopardy and the social order is prostrated. One of the most perplexing problems before society today is the unsettled status of the medical profession in the social structure and the consequent effect upon the health of the people.

Public welfare demands that all levels of society receive adequate medical care, for it is not a luxury but a necessity to every community as well as to every individual. Not all of them are getting it. They should have it. But how? Physicians have contributed millions of dollars every year in medical service to the poor and underprivileged, but it is not enough. It is an obligation of the public and should be provided by taxes or insurance wherever private funds are unavailable.

These questions are not new, nor have they suddenly arisen to bedevil us. The challenge for social change usually arises out of injustice or oppression of some class of society. Such a challenge, although not the first, had its roots in the philosophy of Karl Marx and the rise of

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\*Delivered at the Sixty-sixth Annual Meeting of the American Gynecological Society, at Colorado Springs, Colo., May 26 to 28, 1941.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

of the medical press may not be conducive to dispassionate reasoning when there are primary differences of opinion and approach.

Many plans and schemes have been proposed, some of them apparently feasible and fair, others impractical, many of them savoring of state medicine and some frankly socialistic. Several groups of society are sincerely interested in the solution and honestly believe that they alone have the final answer and look askance at the propositions of all other groups. Health departments inevitably think first of prevention. The physician is likely to think in terms of the private patient, always within the limits of his long cherished rights of individualism and professional freedom. He is impatient with the idea of mass approach, and statistical surveys. The social worker and his statistician are sure their figures answer all questions and solve all problems. The economist is equally sure he can furnish the solution. The sick man doesn't care so long as he gets well—for nothing. All of these group opinions, reached by way of a different approach, lead to divergent views and the solution is not yet. "When doctors disagree, who shall decide?" We all believe in the virtue of the democratic way of composing conflicting opinions by public and unhampered discussion, but it is sometimes difficult to restrain our impatience at the seemingly interminable delays. However, when we recall the inherent complexities of health problems, plus their increasing social aspects, perhaps we should give more sober consideration to the honest views of all concerned. First of all, we must concede that all groups, physicians, health departments, social workers, representatives of government, and the public, are honestly desirous of obtaining, in the American way, greater health security for all of the people without the surrender, by any group, of its freedom and above all, without political, governmental overlordship. Each group has some service of value to contribute. Clear thinking, calm deliberation, sympathetic discussion and lack of emotionalism are likely to lead to action and answers to some of the problems. Other answers may also be found if the fear of experimentation can be overcome.

The settlement of all problems cannot be obtained "out of hand." Some may be composed by cool, dispassionate, judicial discussion among the groups. Others may be tranquillized only by experimentation. The ideas of health insurance are too broad and intricate to be answered dogmatically by its proponents or its antagonists. After all, the health of the whole people is the paramount consideration. The upper income group of the population can secure as good medical care as they are willing to pay for. The indigent group gets reasonable care through tax funds. The near indigent and low income groups present the only real serious problem. The interested groups, public health agencies, physicians, social workers, and economists, all have wrestled with the diverse problems for more than two decades and the end is not in view. It would seem reasonable to expect that a working agreement upon general principles could have been agreed upon long ago.

For purposes of this discussion we are not particularly concerned with the other groups, but we should be much concerned with our own attitudes. "Self analysis is good for the soul." We may well ask ourselves whether we are giving "all-out" service to the solving of the

the feasibility or the advisability of adopting compulsory health insurance. On the other hand, nearly everyone favors voluntary insurance. However, there is still much conflict of opinion as to the various proposed plans; how they may be carried and administered and the basis of equitable costs. The costs of life, accident, and indemnity insurance are determined by actuaries after experience with hundreds of thousands of cases and with such scientific accuracy that there is no doubt about the just premium to be charged. There is very little actuarial experience with any of the plans for health insurance, although some of them were tried on a small scale many years ago. Whether they can be carried for a dollar a month or ten dollars can only be learned by experience, just as the life insurance companies had to learn by actuarial determination. But it can be done by experimentation with health insurance. Health insurance is no exception to the old saw: "There are two sides to every question." You are too familiar with the opposing arguments to justify detailed discussion here.

The feature about these problems that bother me is not the difference of opinion, or that the questions have not been quickly answered, but the too often heard criticism of the medical profession, whether deserved or not. I fear some of it is deserved. It does seem to be opposed to any change in its social status or any alteration of its age-old privileges. No doubt, the public has lost some degree of confidence in the medical profession. I cannot escape the belief that we will serve the public best by increased social-mindedness, less pugnacity, a thorough understanding of the social significance of the problems involved, so that we may take an intelligent, calm, judicial, and sympathetic part in deciding the issues at hand. The fear of social change is well illustrated by the acrimonious debate engendered when the national health insurance bill was introduced into the House of Commons in 1911. The British Medical Association had no voice in its formulation and opposed it bitterly, but Premier Lloyd George forced its passage. However, the experiment was less detrimental to the practice of medicine than anticipated. After the act had been in force seven years, a committee of the British Medical Association made the following surprising report: "The degree of unanimity so far disclosed is somewhat remarkable and suggests that the scheme, which is proving a distinct gain to the medical profession as well as to the public, be still further extended to the dependents of insured persons and for providing, when necessary, specialists, nursing service, hospital treatment, and maternity attendance."

Here we see a very radical medical social change, which by experimentation proved to have at least some merit. Medical social change now has become merely liberal legislation. Not all experiments will prove so salutary, some of them will fail. That lesson will be valuable too.

We cannot afford to have the impression grow that the profession is opposed to every social change. Perhaps we have exhibited too much combativeness and not enough of calm deliberation. It is possible too that the clever sarcasm, high-pitched invective, and evident rage of some

medical profession rightly and jealously guards its professional liberty even to the extreme of being accused and convicted of conspiracy against the public. The medical profession is probably more closely knit and possessed of more power than any other professional group. It is given high privilege because of its healing objectives, its background of higher general education, its necessary special preparation and its code of conduct. The thinking public knows of its high ideals, that it is a group that can and does make science serve the noble art of healing and assuaging suffering. Gratitude usually surrounds the individual physician with an aura which gives to his profession the unique privileges which really place it in a perilous position; for such a gift demands great responsibility and requires great leadership lest it fail to fulfill its sacred trust. The profession has magnificently discharged its obligations to society from the professional standpoint by lowering the general death rate, by decreasing, eliminating, or bringing under reasonable control many dread diseases like tuberculosis, yellow fever, typhoid fever, diphtheria, malaria, pernicious anemia, and very many other diseases. The perils of childbirth to both mother and baby have been reduced 40 per cent and the deaths from infant diseases quite as much. The discovery of the vitamins and endocrines gives a new outlook and hope to suffering humanity. In this developing scientific age, science has been made to serve the sick so that we now dare to speak of scientific medicine. But all of these great accomplishments do not give to organized medicine the right to arrogate to itself the final decision of all questions pertaining to public health, whether medical, economic, sociologic, or questions of sound public policy. Do we, as a profession, sufficiently appreciate that the architecture of the social structure is changing and that there are other quite as necessary building materials as medicine? Unhampered individualism is passing, "believe it or not." Youth, our successors, will not be living in an age like ours, nor meeting the same problems and conditions that we did. "It is a new world." They will find that to master medicine and its allied sciences is not sufficient. In the practice of medicine, sociology has grown to great importance; indeed, medicine itself has become a social science; therefore it cannot possibly escape the impacts of changing social attitudes which will confront the younger generation of physicians with increasing force and will require of them to possess a much greater social consciousness than we have ever had.

Unfortunately, medical students have little or no preparation in the social sciences, such as history, political science, sociology, or economics, which are so necessary for social understanding and training for citizenship; and, as I see it, particularly for entering the practice of medicine which, in the future, will have an ever increasing and profound social significance. We want our intellectual medical progeny to cling to the splendid traditions of the profession, while becoming less class-conscious and individualistic, but at the same time more open-minded and aware of the interested concern of the public in matters of health. This new generation has been well trained and inspired by the best teachers to high ideals of service and research, so we need have

problems. Is the impression correct that the medical profession is constantly antagonistic or at least negative in its attitude? Is the profession in a state of social or unsocial torpor? Are these questions going to be answered without the cooperation of the profession, as were the workmen's compensation laws? Shall we permit a constructive health program for all the people to be formulated without our participation? We, of a so-called learned profession, may think much, perhaps overmuch, of our professional liberty. We shall fail in our full duty if we forget that ours is a profession; not a business, not a trade, but a calling, which implies public service. The public is so vitally interested in the practice of medicine that it looks upon it almost as a public utility. Hence, the public must be taken into our confidence and sympathetic consideration; otherwise we may be compelled to submit, as have the utilities companies, to public control. There ought to be a common ground upon which the saner elements of society could meet and make common cause with the profession so that justice might be done to the public and to the physician.

Organizations in the interest of groups have an increasing importance in the society of today; manufacturer and merchants' associations, farmers' leagues, labor unions, consumers' cooperatives, and societies of the learned professions now all act through organizations, the members of which often have more intense loyalties to their particular organization than to their political party or even patriotism to the country. Many of them date back to the medieval craft guilds like the guild of barber-surgeons, the forerunner of modern medical societies. In these, special privileges were established in the middle ages and added to from time to time by custom, tradition, and law. These privileges were granted by society, not as a right, but as a trust, because each one could perform some service to society better than others. Physicians were granted the special privileges of self-government, authority to control admission to membership and discipline; and adoption of rules of conduct (ethics) because members of their organization, only, could be entrusted to deal with health, life, and death and because to perform these duties a broad education, special preparation, and skill were required. Such privileges, accorded by society, impose obligation upon the recipient of giving back to society forever the service for which they were bestowed. If the organization forgets its ideals and descends to the level of self-interest, it endangers its liberty of action in society.

If our profession shows wisdom in adjusting itself to social changes by loyalty to the general welfare of the people and freedom from selfish professional interests, it will surely retain its cherished historic liberties. Otherwise society may withdraw the privilege. Privileges are too often looked upon as inalienable rights: Industry presumes to dictate wages and labor conditions, labor assumes the right to sit down and capture a plant or maim the "scab" and both labor and capital can assume the attitude of "the public be damned" or the medical profession can say: "Avaunt with all your social changes—we will practice medicine as we please, as we have always done." Privileged organizations must realize that the days of "the public be damned" are gone. The

## PROLIFERATIVE CHANGES IN THE SENILE ENDOMETRIUM\*

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THE traditional concept of the senile endometrium is of a mucosa which, having been deprived of its estrogen maintenance, has become thin and atrophic, with sparse, shrunken, and sometimes cystic glands, and with a scant fibrotic stroma. A number of authors in recent years have called attention to the fact that this is by no means always the case, and these observations have appeared to fit in with the now well-established fact that estrogen may be found in the urine of women long after the menopause or after castration.

The production of estrogen during the postmenopausal epoch would seem to explain the occurrence of proliferative endometrial pictures of one degree or another, especially since it is well known that the postmenopausal endometrium, unlike the postmenopausal ovary, is capable of reactivation by means of hormone stimulation. For this there is abundant evidence, both experimental (Clauberg, Kaufmann, Loeser) and clinical. The administration of adequate amounts of estrogen even to castrated women will produce a typical hyperplasia. For that matter, even a typical secretory endometrium can be produced in such women by the sequential injection of estrogen and progesterone. As an extreme example, Hübscher was able, by means of estrogen and progesterone, to reproduce a progestational histologic cycle in a woman of 80 years. From a clinical standpoint, the endometrial responses brought about in postmenopausal women by the functioning feminizing tumors of the granulosa-cell and thecoma groups constitute good illustrations of the responsiveness of the senile endometrium to the ovarian hormones.

By contrast, the evidence indicates that the ovary, once it has reached the end of its life span at the menopause, is not capable of re-activation by any means of hormonal stimulation. Only Westmann has reported contrary results in one case, but his observations have apparently been quite effectively refuted by the work of Tsehertok and Penkow, Waldeyer, and others.

As to the source of the postmenopausal estrogen, there is as yet no certainty. There are still many who believe that such estrogenic sex sterols may be chemical metabolites of certain body sterols, with cholesterol as the probable mother substance. The fact that estrogens have been shown to be produced in other endocrine glands than the ovary, especially in the adrenal cortex, has led to the growing view that some such extraovarian endocrine gland source is responsible. The finding of estrogen long after complete removal of the ovaries, as well as

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no anxiety about their progress in medicine and its allied sciences. Neither need we be solicitous about their ethics, the philosophy of morals, for after all, ethics is merely doing the right thing by one's patient, colleagues, and the public. But I confess that I still have some apprehension as to their social consciousness, for I am not sure that the most individualistic of the learned professions has left them a great legacy of social understanding.

Medical teachers allied with scientists insure the progress of medicine. The need is for its application to all the people. That is the great ideal. We hope it is not too far in the future. To accomplish it great leadership must take command. In the past there have been too many politicians and not enough diplomats. When the people are convinced that they are wisely led by medical statesmen and that the profession itself is imbued with unselfish, practically applied ideals and is inspired by lofty social understanding, mankind will reverently and with deep gratitude gladly accord to the medical profession all of the intrinsic values of its traditional professional liberty.

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Other hypotheses, none very satisfying, have been suggested to explain the bleeding seen in association with some cases of the non-specific types of ovarian tumors. Moulouguet-Doléris, for example, believed it to be due to a trophic effect on the endometrium resulting from the effects of the tumor on the ovarian nerve plexus, while Wehse suggested as the responsible factor the ovarian metabolic changes induced by the growth. Tietze ascribes the important role to the metabolic and vascular changes produced by the tumor, while Meyer stresses the possible role in at least some cases of a co-existing or incorrectly interpreted functioning neoplasm.

Our own opinion, based on the study of a good many cases, is that ovarian tumors, with the exception of those known to have definite endocrine-producing function, have no characteristic effect on the endometrium. Since, however, there is some difference of opinion on this point, we have excluded such cases from our material with the exception of one or two cases mentioned below, which illustrated certain points and in which it was reasonably certain that no noteworthy effect on the endometrium could be produced by the tumor.

Our present study is based on the microscopic examination of 137 postmenopausal endometria obtained either by curetting or hysterectomy. No especial selectiveness was exercised, except to eliminate those cases in which the material was too scanty to permit of histologic conclusions and those in which there were associated lesions, more particularly ovarian tumors, in which a modification of endometrial histology by the lesion was at least theoretically possible. On the other hand, a number of cases are included in which simple inactive ovarian lesions, such as germinal inclusion cysts or retrogressed endometrial cysts, were present. Moreover, in a good many cases uterine lesions, such as small or moderate myomas, were present, as it is difficult to believe that they would exert any important effect on the endometrium. Finally, in 10 cases carcinoma of the cervix was an associated lesion, while cervical polyps were present in four. These conditions were assumed to be the cause of any bleeding which was noted in the clinical review of the cases in our series.

The elimination of cases in which curetting has yielded such scant tissue that satisfactory histologic examination was impossible should be stressed, because there is no doubt that many if not all of these represented extreme atrophy of the endometrium. In Breipohl's study this assumption was actually made, but it did not impress us as fully warranted. This point obviously has a bearing on the incidence of the atrophic type of endometrium in our series, as something like 20 cases were eliminated from the series on this account. No case is included in which there was an interval of less than two years between the last menstrual period and the time of operation.

It is a well-known fact that ovarian activity, as indicated either by irregular normal ovulatory cycles or by persistence of hyperplasia and other lesser degrees of growth activity, may continue for a considerable

the histologic study of senile ovaries, would seem to exclude the latter from consideration as sources of postmenopausal estrogen.

The present study, however, has to deal with the histologic rather than the hormonal aspects of this problem. In a previous paper (1936) from this laboratory (Novak and Yui) in which no less than 804 cases of hyperplasia were studied, 40 were found to have occurred beyond the menopause. In 1932 Taylor had also described the occurrence of hyperplasia postmenopausally. In both of these papers, however, as well as in the more recent paper of Taylor and Millen, these findings constituted a by-product in the study of the broader problems of adenocarcinoma or postmenopausal bleeding.

Perhaps the most direct study of the endometrium in a large group of cases of postmenopausal bleeding is that of Breipohl (1935), whose material consisted of 130 postmenopausal endometria from women over forty-five years of age and at least six months after the last menstruation. In 76 of these, the mucosa was atrophic, including in this group 11 in which practically no tissue was removed, and 4 in which it was described as necrotic. Adenocarcinoma was found in 22 cases while in fully 31 cases there was evidence of proliferative activity. This latter group embraced 15 cases of hyperplasia (including 2 with granulosa cell carcinoma of the ovary), 11 in which the endometrium was described as corresponding to a proliferative phase, and 3 in which secretory endometrium was found. This last-named group must be viewed with skepticism as applied to the senile endometrium, because of the fact that Breipohl included in his study patients in whom the menopause had occurred only six months previously. There is no doubt that menstruation and ovulation may occur after much longer intervals than this. Unfortunately he gives details of only one of these three patients, and in this the interval after the last menstruation was only one year, the patient being fifty years of age. He emphasizes, however, that more than one year had elapsed since the menopause in 26 of the entire proliferative group of 31, and in 9 more than ten years had elapsed.

Closely related to this question of postmenopausal hyperplasia in the case of women with grossly normal pelvic organs is that of the endometrial changes and the endometrial bleeding which have been described in association with various tumors of the ovary. The role of the estrogen-producing tumors (granulosa cell carcinoma and thecoma) in this connection is now universally accepted, and needs no elaboration here. Much less clearly explained is the uterine bleeding which occurs in a small proportion of ovarian tumors of other types, such as carcinoma, fibroma, cystadenoma, and Brenner tumors. Studies on this question have been made by a good many authors (Schiffman, Lahm, Meyer, Moulonguet-Dol  ris, Wehse). Some, like Schiffman, described hyperplasia of the endometrium in association with various tumors, to which they were inclined to ascribe a hormone-producing effect, although such tumors are not commonly accepted as having any such effect. The relative frequency of postmenopausal hyperplasia in the absence of any tumor would seem to cast doubt on such an assumption, and to favor the view that such ovarian tumors and hyperplasia might co-exist without any relation of cause and effect.

however, the ovaries presented the characteristics commonly attributed to the senile ovary. This is in conformity with the results obtained by Novak and Yui in the examination of 26 ovaries from cases of postmenopausal hyperplasia. These negative histologic findings do not exclude the possibility of postmenopausal production of estrogen by some ovarian element, but they make it seem unlikely.

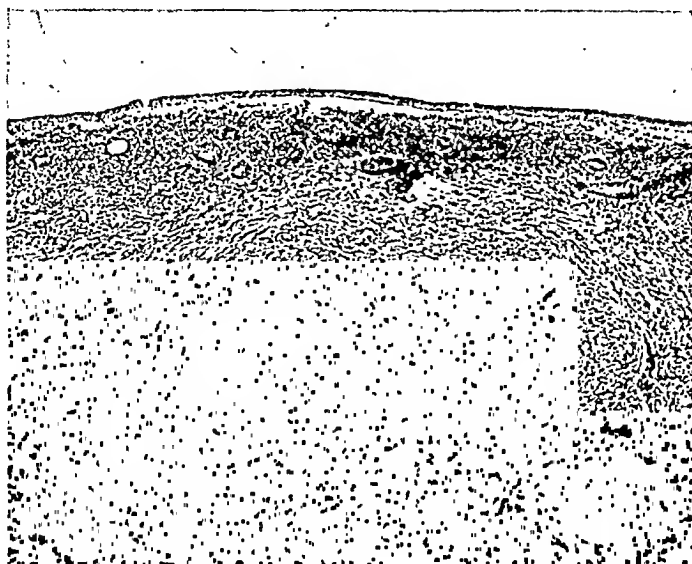


Fig. 3.—Atrophic endometrium six years after menopause, in patient of 55 years.



Fig. 4.—Moderately proliferative endometrium twenty-four years after menopause, in patient of 61 years.

At the outset it may be stated that the traditional concept of the senile endometrium as a very atrophic tissue was borne out in less than half of our cases, 62 out of 137. On the other hand, in a substantial proportion, varying degrees of proliferative activity were observed. The

time after the last menstrual flow. Rarely, however, would one expect evidence of this functional ovarian persistence for much over a year, so that the two-year limit which was arbitrarily chosen for our series seemed like a fair one as indicative of the postmenopausal status. Moreover, the majority of our cases, as will appear below, were women in whom the

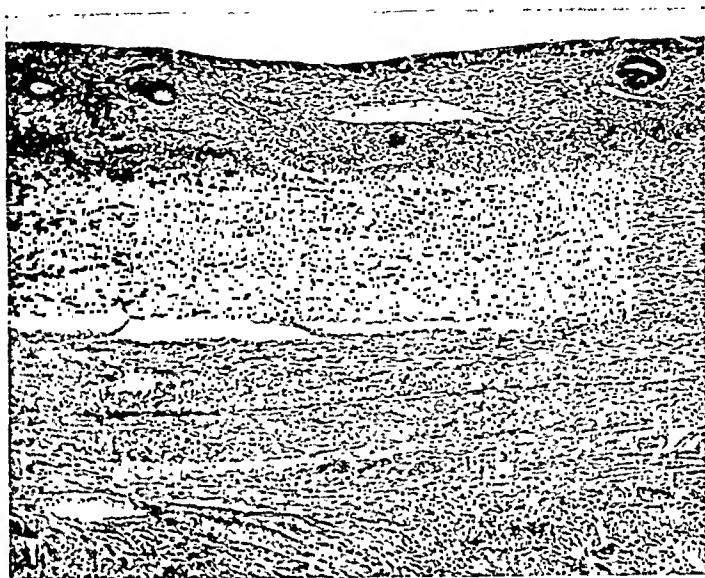


Fig. 1.—Atrophic endometrium four years after menopause, in patient of 52 years.

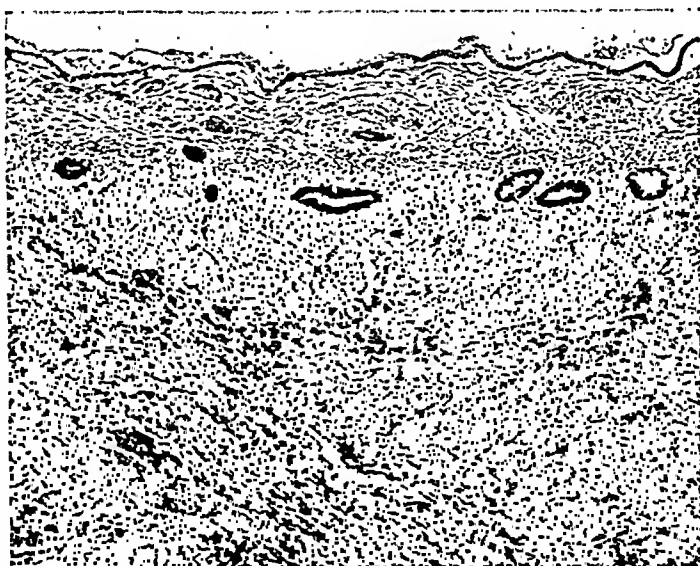


Fig. 2.—Atrophic endometrium nine years after menopause, in patient of 58 years.

postmenopausal span was much longer than two years. In only a fraction of our cases were the ovaries available for study. We are presenting no detailed report of the ovarian findings, but, suffice it to say, no histologic evidence could be obtained to indicate any persistence of ovarian function long after the menopause. This would not apply to ovaries removed within a year or two after the menopause. As a rule,

Swiss cheese gland pattern, an intact epithelium with often dark-staining nuclei, and an abundant compact stroma (Figs. 5 and 6).

While the above three groups were those originally outlined for our review, we soon found that a fourth and well-defined type of endometrium kept recurring very frequently. To this we have applied the designation of

4. Retrogressive hyperplasia. In this the Swiss cheese pattern is perfectly marked, but the inactivity and retrogressiveness of the process is indicated by the fact that the epithelium is often low and atrophic, and the stroma obviously fibrous and inactive, so that with the ordinary hematoxylin-eosin stain the stromal fields stain pink instead of the

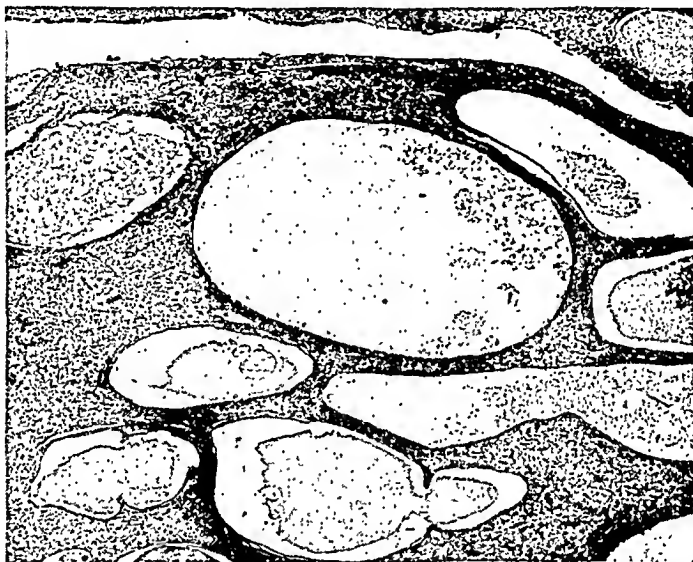


Fig. 7.—Retrogressed hyperplasia ten years after menopause, in patient of 51 years. Note flat epithelium and fibrous stroma.

dominant blue of the active hyperplasia. In passing it may be added that the fibrotic appearance of the stroma appears a more reliable indicator of hormonal inactivity than does the epithelium, which may remain tall and active-looking for many years after the menopause, even when the stroma is very fibrotic (Fig. 7).

#### THE HISTOLOGIC PATTERN IN DIFFERENT AGE GROUPS

It seemed advisable, if we were to study the postmenopausal history of the endometrium, to divide our cases into age groups, in order to determine whether any particular pattern can be correlated with any age subdivision. It was quite obvious, as will appear below, that this is not the case, and that the most conspicuous finding on such a correlative study is the hopeless disparity of the findings in this respect. In some women the endometrium is extremely atrophic within a year, sometimes only a few months after the last menstrual period, while in others the mucosa of women thirty or forty years after the menopause may be the seat of an active hyperplastic process indistinguishable from that seen so often during reproductive life.

most sensible plan of grouping the cases histologically appeared to be the following:

1. The thin atrophic mucosa, in which the surface and gland epithelium is either of normal height and appearance or flattened, the stroma more or less fibrotic, and the glands sparse and not infrequently cystic (Figs. 1, 2, and 3).



Fig. 5.—Typical Swiss cheese hyperplasia ten years after menopause, in patient of 50 years.

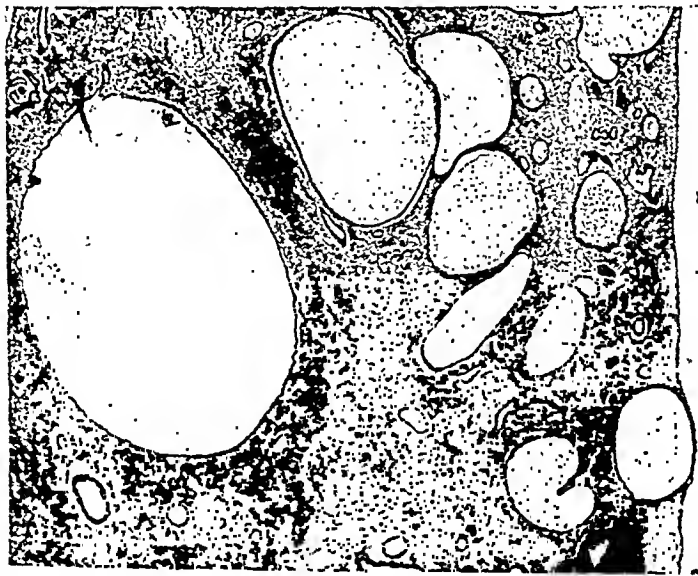


Fig. 6.—Active hyperplasia twenty-one years after menopause, in patient of seventy-one years.

2. Moderately proliferative pictures like those seen during reproductive life in the follicular (postmenstrual or early interval) phase of the cycle (Fig. 4).

3. Outspoken and apparently active hyperplasia identical with the hyperplasia of the reproductive phase of life, and characterized by the

The group of 17 cases from ten to fifteen years after the menopause embraced 10 atrophic endometriums, none with moderate proliferation, 1 with hyperplasia, and 6 with retrogressive hyperplasia. In this group the age variation was 56 to 67 years.

Finally, there was a group of 26 patients in whom the menopause had occurred more than fifteen years previously, including 2 in whom 40 years had elapsed since the last menstruation (ages 80 and 87). Only 11 of this group showed typical atrophy, while 4 showed moderate proliferation, 9 definite hyperplasia, and 2 retrogressed hyperplasia. The most remarkable group was that showing hyperplasia, and it is of interest to note that this occurred with especial frequency in the oldest members of this group (Figs. 8 and 9). The ages of these 9 patients were 87, 80, 73, 71, 70, 66, 62 (2 cases), and 50. On the other hand, the youngest member of this group, a patient of 49 years who had had a premature menopause sixteen years previously, showed a marked endometrial atrophy.



Fig. 10.—High power picture of another area in case shown in Fig. 9. Note mitoses and stratification in epithelium.

Adding these groups together, it is seen that the classification of the endometriums in the entire series of 137 postmenopausal cases is as follows: atrophic 62, moderate proliferation 14, hyperplasia 28, and retrogressed hyperplasia 33. Fully 42 (28.3 per cent) endometriums, therefore, embracing the moderately proliferative and hyperplastic groups, showed a degree of proliferative activity comparable to that seen during the reproductive epoch, while those in whom there was evidence of active hyperplasia comprised 28 (19.2 per cent). In the majority of these cases, however, the hyperplasia was not uniform throughout the sections which were available to us for study. In those in whom hysterectomy had been done, and in whom blocks of the uterine wall were available, it was often seen that the hyperplasia occurred in large patches in an endometrium which otherwise showed only slight proliferation or even atrophy, and in some cases there was a tendency to polyp formation. We feel sure, however, that anyone examining



Of our 137 cases 63 were from two to five years (inclusive) beyond the menopause. The endometrium in 28 of these was atrophic, while in 10 it showed a moderate proliferative picture, in 11 hyperplasia, and in 14 a retrogressed hyperplasia. The ages of these patients varied from 39 to 60 years.

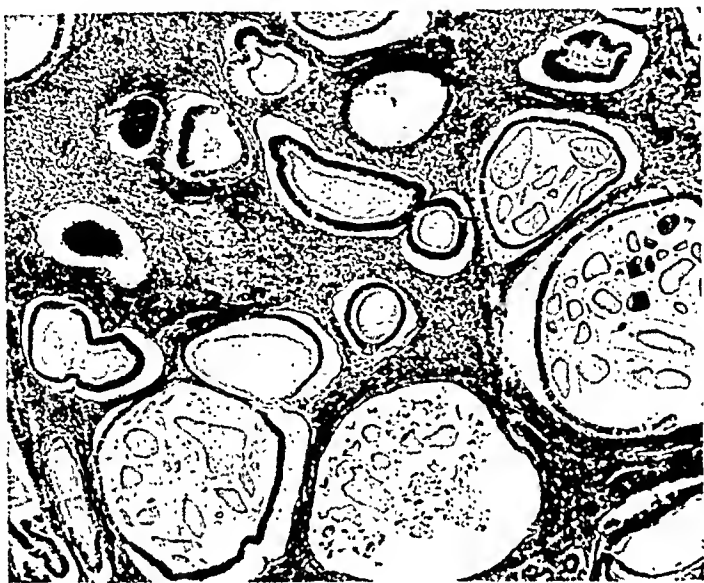


Fig. 8.—Typical active hyperplasia forty years after menopause, in patient of 57 years.

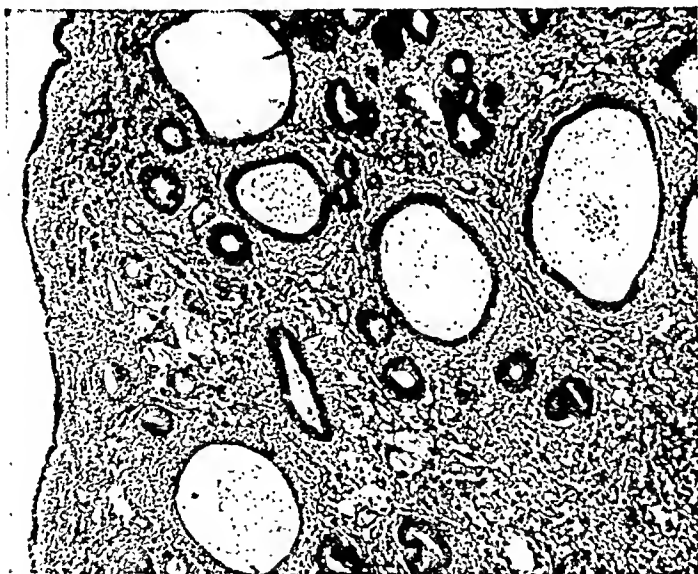


Fig. 9.—Active Swiss cheese hyperplasia thirty years after menopause, in patient of 50 years. See high power of mitoses in epithelium (Fig. 10).

In the group of 31 cases from five to ten years postmenopausal, the endometriums were classed as atrophic in 13, moderately proliferative in none, hyperplastic in 7, while the remaining 11 showed retrogressed hyperplasia. The ages of the patients in this group varied from 45 to 65 years.



when it cannot be palpated, as was once urged by some. As our study indicates, postmenopausal hyperplasia not infrequently exists in the absence of tumors of any kind. Furthermore, when hyperplasia is found with ovarian tumors of nonendocrine character, there is far more likelihood that the two lesions are coincidental rather than that the ovarian tumor is responsible for the endometrial change.

Finally, bleeding was a symptom in 8 cases (eliminating 1 case of cervical carcinoma) of the 33 in which a retrogressed hyperplasia of the endometrium was found. In some of these the endometrial condition was found only in old polyps, and it is possible that ulcerative changes in the polyp might have been responsible for the bleeding. Since the hyperplasia pattern in all cases was obviously an inactive one, there is no justification for invoking hormonal factors in the explanation of this type of bleeding.



Fig. 11.—Hyperplasia fifteen years after menopause, in patient of 62 years. The presence of an ovarian tumor which proved to be a simple fibroma led to preoperative diagnosis of granulosa cell carcinoma.

The chief interest of this rather considerable group of retrogressive cases would seem to be that they indicate the remarkable persistence of the typical Swiss cheese gland pattern, often for many years after the menopause, and quite possibly throughout the life of the woman. Once this pattern is stamped on the endometrium, as it so often is at the time of the menopause, it appears to remain in a sort of fossilized form thereafter. Menopausal hyperplasia results from an aberration or exaggeration of the anovulatory mechanism, and we believe that the finding of retrogressed hyperplasia long after the menopause is good retrospective evidence that the terminal menstrual mechanism was anovulatory. On the other hand, the finding of an atrophic endometrium would suggest that menstruation and ovulation had come to an end at about the same time; that is, that ovulation had continued to the very end of menstrual life.

these sections would agree that the hyperplastic areas were indistinguishable from those seen during reproductive life. In a number the activity of the hyperplastic process was further indicated by the finding of mitoses in the epithelium or stroma, more often the former (Fig. 10).

#### CLINICAL BEARING

The only clinical symptom which one would think of in relation to postmenopausal endometrial proliferation is bleeding. As regards the atrophic group, suffice it to say that bleeding was a symptom in 29 of the 62 cases of this type (7 cases of cervical carcinoma and 1 of cervical polyp eliminated), and in most of these it constituted the indication for diagnostic curettage. In practically every one, however, the bleeding was of very scant or spotting character, the duration varying between two days and two years. In other words it represented the type of postmenopausal bleeding which we characteristically associate with so-called senile endometritis. In many of our cases evidences of inflammatory infiltration were evident on microscopic examination. The bleeding in such cases probably has its source in tiny superficial areas of the atrophic endometrium, similar to those which can be visually demonstrated in senile vaginitis.

No such explanation would seem applicable to the proliferative group, and yet many cases of this group were characterized by bleeding. No less than 10 of the 14 moderately proliferative group (1 case of cervical carcinoma and 1 of cervical polyp eliminated), and no less than 12 of the 28 cases in the hyperplasia group (eliminating 1 case of cervical carcinoma and 2 of cervical polyp) were characterized by bleeding, in some cases slight, in others fairly free and sometimes of rather long duration. Since no other factor than the endometrial lesion could be demonstrated in these cases, the significance of postmenopausal proliferation in the endometrium as a possible cause of postmenopausal bleeding is evident. There would seem to be little doubt that this type of bleeding is due to a hormonal mechanism similar to that which brings about the functional bleeding of the reproductive era.

One especially interesting case was included in this group notwithstanding the fact that an ovarian tumor was present. This patient, (case of Dr. R. W. TeLinde), was 62 years old, and had had bleeding for eight months. The preoperative examination disclosed a tumor about the size of a large orange in the ovary. A curetting was done before laparotomy, and this revealed a typical hyperplasia of the endometrium (Fig. 11), so that it seemed highly probable that the ovarian tumor was of granulosa-cell character. However, it proved to be a typical solid fibroma with no suggestion of granulosa or thecal elements.

This case is instructive as emphasizing again the fact that the finding of endometrial hyperplasia in postmenopausal women is not by any means indicative of the granulosa or thecal character of an ovarian tumor, should one be present. Far less does such an endometrial picture warrant the assumption that a tumor of this sort is present even

the hyperplasia pattern still persists, although the markedly retrogressive changes in both stroma and epithelium leave no doubt as to the vestigial nature of the process.

One other point deserves mention as regards this inactive, residual hyperplasia pattern which we have encountered so frequently. Most writers stress the frequency of cystic distention of the glands as a feature of senile atrophy of the endometrium, attributing this to occlusion of the ducts by the stromal shrinkage or by inflammation. While this is undoubtedly true in some cases, we do not believe it explains the majority of instances in which marked cystic distention of the glands is found postmenopausally. We are convinced that in the majority of such cases we are dealing with a persistence of the cystic gland enlargement which forms a part of the Swiss cheese hyperplasia pattern (Figs. 12 and 13). We base this view not only on the similarity of the gland pattern, but also on the fact that we have observed all grades of transition between the active and inactive grades of hyperplasia.

#### SUMMARY

A study was made of 137 endometriums from women ranging from 2 to 40 years after the menopause. Less than one-half of these, 62 cases, showed the atrophic changes usually looked upon as characteristic of the senile endometrium. Fully 42 presented pictures of proliferative activity, moderate in 14, while 28 showed considerable areas of outspoken hyperplasia similar to that seen so often during reproductive life. These findings are no doubt to be linked up with the well-known fact that estrogen may be produced long after the menopause. The source of this postmenopausal estrogen is not definitely known, though it seems reasonably certain that it is not in the ovaries, but rather in some of the other endocrine glands, probably the adrenals.

The endometriums in this series were studied in age groups, showing a striking lack of correlation between the ages of the patients and the histology of the endometrium. The mucosa of some women may show marked atrophy within a few months of the last period, while that of others, 30 or 40 years later, may show striking hyperplasia. The latter, for example, was found in 5 women of 70 or over, the oldest being 87 years.

The clinical importance of these findings lies in the fact that postmenopausal bleeding is a not infrequent symptom in such cases, and it would seem likely that it is due to a hormonal mechanism like that involved in the common functional hemorrhage of the reproductive era.

The remaining 33 cases of this series revealed a histologic picture which we consider to represent a retrogressed hyperplasia. It is characterized by a typical Swiss cheese pattern, but with obvious evidence of retrogression and inactivity, such as fibrosis of the stroma. The significance of this endometrial pattern is that the hyperplasia pattern found in a large proportion of menopausal women persists for many years thereafter, although the causative hormonal factor is no longer operative. Finally, our findings suggest that this residual hyperplasia,

Putting our observations together, we would suggest that the varied postmenopausal histology of the endometrium merely reflects the variations in the terminal functional activity of the ovary. If menstruation and ovulation both cease rather abruptly, an atrophic postmenopausal

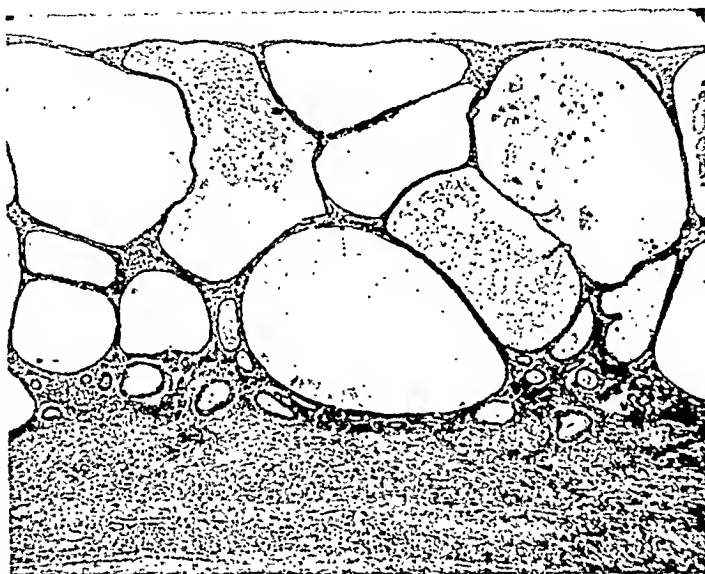


Fig. 12.—Retrogressed hyperplasia three years after menopause, in patient of 57 years. Note extreme cystic enlargement of glands.

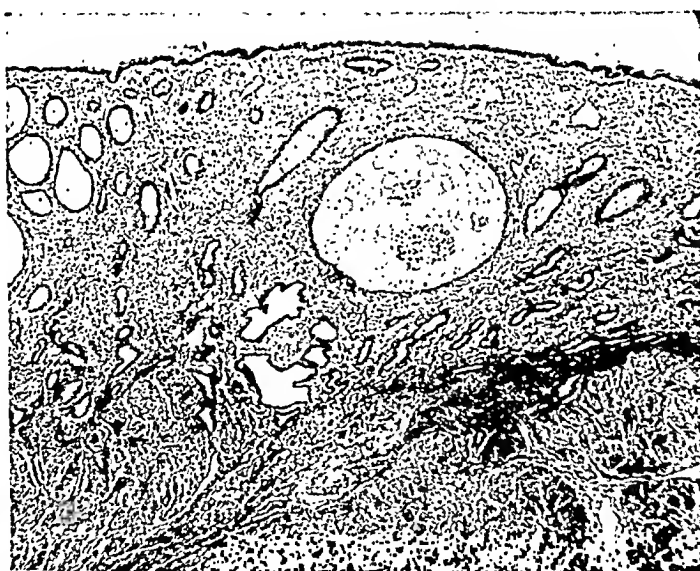


Fig. 13.—Retrogressed hyperplasia, with persisting cystic glands, seven years after menopause, in patient of 49 years.

endometrium may be expected. If, as is so often the case, the terminal cycles are anovulatory, and especially if they are associated with a terminal hyperplasia, as is also common, the hyperplasia pattern may persist for a considerable period of time after the menopause, even in the absence of postmenopausal bleeding. After a variable and indeterminate period, with the complete cessation of estrogen production,

It is not possible to say from histologic examination whether or not these cells have any estrogenic power. Small to medium-sized follicular cysts are not infrequently found in senile ovaries, sometimes in association with endometrial polyps. The cortical stroma even in completely senile ovaries maintains its peculiar cytologic character.

*Second*, attempts to apply chemical reactions for estrogens to tissue staining, with the object of identifying estrogenic cells, have so far ended in failure.

*Third*, slices of human ovary were implanted intraperitoneally in spayed female white rats. With some exceptions, when premenopausal ovaries were used, estrus resulted on the sixth day. Postmenopausal ovarian tissue gave no detectable estrogenic effect. Our series is too small to permit conclusions, but is being extended, and we hope to carry it further.

Drs. Novak and Richardson's paper covers a very important practical field and serves to emphasize the necessity for thoroughgoing study of postmenopausal bleeding.

We believe that it remains to be proved that the senile ovary does not exert some endocrine influence, although it appears entirely possible that estrogenic substances may be formed in the adrenal or elsewhere in the body.

Does endometrial hyperplasia occur in castrates? Our own files do not supply enough cases to answer this question. Also the question raised by Herrell as to whether corpus carcinoma occurs in castrates is pertinent here.

Drs. Novak and Richardson suggest that the varied postmenopausal endometrial picture reflects the variations in the terminal functional activity of the ovary, and we are in accord with this viewpoint, believing that estrogenic activity may persist for a variable time after ovulation ceases.

DR. J. HOFBAUER, CINCINNATI, OHIO (by invitation).—The experimental reproduction of the pattern of endometrial hyperplasia by the repeated intramuscular implantation of bits of anterior pituitary substance (Hofbauer, Surg., Gyn. & Obst., 1931) represented the first attempt to demonstrate that the anterior pituitary registers its intensified effect upon the uterine mucosa through the mediation of the ovary. Subsequently in ovariectomized guinea pigs, using the same experimental technique, proliferative lesions of the basal layer of the uterine mucosa were produced (Hofbauer, J. Obst. & Gynaec. Brit. Emp., 1939).

Such animals showed hyperplastic changes in the adrenal cortex. Hence, it may be assumed that, in the menopause, the proliferative endometrial changes observed may result through the action of estrogenic substances known to be elaborated in part in the adrenal cortex.

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—The assumption seems to have been made that late epithelial proliferation of the endometrium must be due to a persistent or recurrent estrogenic function. Such proliferation may, however, be caused by other types of stimuli, perhaps localized in the uterus such for instance as that which causes polyps. It is indeed possible that some of these signs of proliferation reported by Dr. Novak are localized tissue changes similar to that seen in polyps but which have not attained the polypoid form.

I would like to ask Dr. Novak whether the proliferative changes reported by him were widespread throughout the endometrium, or were more localized. In the latter case the proliferation might represent the beginnings of polyps or similar sessile growths and not a general endometrial response such as one would expect from a hormone stimulus.

DR. HERBERT F. TRAUT, NEW YORK, N. Y.—For some years we have been making routine vaginal smears in all our patients and we have of course dealt with a large number of women in the postmenopausal period. We have learned that there is a tremendous difference in the response of the cervical and vaginal cells which find their way into the smears. These variations are not entirely dependent upon the available estrogen. There seem to be factors other than the estrogen which have much to do with the function of the female genital tract. What those factors are we do not know, but we have many reasons to believe that the menopause is characterized by different hormonal stimuli taking over as the estrogens pass out of the picture more or less completely.

rather than inflammation or stromal cicatrization, is the most frequent explanation of the cystic gland distention so often seen in senile endometriums.

#### REFERENCES

- (1) *Hübscher, K.*: Zentralbl. f. Gynäk. 57: 2844, 1933. (2) *Westmann, A.*: Ibid. 58: 1090, 1934. (3) *Tschertok, R. A., and Penkow, G. W.*: Monatschr. f. Geburtsh. u. Gynäk. 97: 146, 1934. (4) *Waldeyer, L.*: Zentralbl. f. Gynäk. 58: 2882, 1934. (5) *Novak, E., and Yui, E.*: AM. J. OBST. & GYNEC. 32: 674, 1936. (6) *Taylor, H. C., Jr.*: Ibid. 23: 309, 1932. (7) *Taylor, H. C., Jr., and Millen, R.*: Ibid. 36: 22, 1938. (8) *Breipohl, W.*: Zentralbl. f. Gynäk. 59: 1998, 1935. (9) *Schiffman, J.*: Ibid. 51: 2098, 1927; Arch. f. Gynäk. 150: 159, 1932. (10) *Moulouquet-Dolérès, P.*: Gynec. et obst. 9: 493, 1924. (11) *Wehse, A.*: Inaug. Diss. Breslau, 1924, Quoted by R. Meyer (see ref. 13). (12) *Tietze, K.*: Arch. f. Gynäk. 146: 197, 1931. (13) *Meyer, R.*: Zentralbl. f. Gynäk. 49: 1662, 1925.

26 EAST PRESTON STREET

#### DISCUSSION

DR. CLARENCE B. INGRAHAM, DENVER, COLO.—Assuming that postmenopausal endometrial hyperplasia is the result of estrogenic stimulation, the question of the source of the hormone remains to be answered.

It is not certain that the estrogenic substance found in postmenopausal women and in castrates is identical. It is certain in either case that the supply of hormone is not sufficient to prevent genital atrophy.

Novak and Yui concluded that estrogenic function is probably lacking in senile ovaries. On the other hand, Wallart believes that the menopause signifies cessation of ovulation only and not complete involution.

Herrell states that corpus carcinoma is the result of ovarian estrogenic influence. Carcinoma of the body of the uterus has never been seen, as far as *he* could determine, in a previously castrated individual.

Granulosa and theca cell tumors, and adrenal cortical tumors, are derived from cells having a common embryonic source. The tumor cells can produce sex hormones at any age, before puberty or after the menopause. Estrogenic substance has been extracted from the adrenal cortex. Thus a close relationship must exist between the adrenals and gonads.

Hypothalamic lesions may be associated with precocious puberty. It has been shown by Brooks that transection of the pituitary stalk prevents ovulation in rabbits. Here are indications of a nervous system control of gonadal function, perhaps mediated through the pituitary. It is possible that there is a neuroendocrine difference between the postmenopausal woman and the castrate.

The source of estrogen in the ovary has been shown to be the theca interna cell. Precocious puberty due to an ovarian follicle cyst has been reported by W. F. Mengert. This calls attention to the functional activity of atretic follicles, follicle cysts, and so-called interstitial cells. Maximow and Bloom state that interstitial cells originate from the theca interna of atretic follicles. In the human ovary they soon degenerate and disappear. However, they state also that ovarian stroma cells are not ordinary fibroblasts, being capable of giving rise to other cell types, to decidual cells, to interstitial cells, etc.

Parks, using mice, and Schmidt, using guinea pigs, found growths of cords of epithelioid cells in the ovaries following x-ray, and estrus was not abolished. Schmidt thought the epithelioid cells were the source of estrin. More recently Butterworth found granulosa cell tumors in the ovaries of senile mice following x-ray, apparently developing from normal follicles, following degeneration of the ova.

Such findings as the foregoing led us to inquire into the problem of postmenopausal ovarian activity. Dr. Black and Mr. Polsky of the Pathology Department of the University of Colorado, and I have approached this problem in several ways. First, by applying the Foot reticulum stain to a histologic study of senile ovaries, after the plan of Traut and Marchetti in dealing with granulosa cell tumors. They found that with the reticulum stain they could distinguish theca cells, and that most granulosa cell tumors contain them. We found that theca cells can be demonstrated in postmenopausal ovaries, but that they lie singly or in small groups, and that they are not numerous except in granulosa cell tumors.

# A COMPARATIVE ANALYSIS OF TOTAL ABDOMINAL, SUPRAVAGINAL, AND VAGINAL HYSTERECTOMIES\*

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THIS study comprises a survey of hysterectomies done on the Tulane University Gynecological Service of Charity Hospital, during the years 1939 and 1940. The series represents a total of 828 consecutive hysterectomies. We purposely divided and kept segregated the data obtained from each of the two years' work studied, in an effort to prove the definite, growing conviction that total hysterectomy, either by the transabdominal or the vaginal route, warrants its position of priority. A separate analysis of the white and colored services was undertaken in order to attempt an evaluation of the relative safety of the three types of hysterectomy in the colored woman, in whom the pathology which necessitates surgery is always of a more gross and extensive nature.

The evidence accumulated through the study of this and other large series of hysterectomies, leaves little basis for controversy as to the relative superiority of total over supravaginal hysterectomy in most cases. Complete removal of the uterus, where such surgery is indicated, has become increasingly popular and is the method of choice with most gynecologists for several reasons: (1) The mortality and morbidity rates for total hysterectomy are as low as, or lower than, those encountered in an equal number of supravaginal amputations. (2) In from 12 to 15 per cent of the cases in which the cervix is not removed, intractable leucorrhea, pelvic pain, and backache cause the patient to return subsequently for cauterization, conization, or removal of the cervical stump. (3) The cervix may harbor a focus of infection from which such metastatic lesions as arthritis, myositis, and iritis may result. (4) The frequency of the development of carcinoma on the cervix following subtotal hysterectomy is difficult to estimate; the literature records the incidence variously as from 1 to 7 per cent. Even if the smaller figure is correct, such a cancer risk should obviously influence the gynecologist to select the complete type of operation in all cases where it is feasible.

Prolapse of the vaginal vault, shortening of the vaginal canal, and dyspareunia are objections which have been offered to total hysterectomy, but which we feel have little valid justification. No apprehension need be felt that a prolapse of the vagina may occur following complete hysterectomy if the severed cardinal, uterosacral, round, and broad ligaments are sutured accurately to the lateral margins of the vaginal cuff, and if a reconstruction of the perineal and bladder supports is also done.

\*Read at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

DR. NOVAK (closing).—Most of the discussion has centered around that aspect of the paper which we least emphasized and concerning which we know little, namely the nature and the source of the estrogenic stimulus responsible for the postmenopausal proliferative changes in the endometrium. While the senile ovary may be the source of the causative estrogen, we think this very unlikely, for reasons we have discussed in our paper. An origin from one of the other endocrine glands, perhaps the adrenal cortex, seems more likely.

The hyperplasia of postmenopausal life is often localized. During reproductive life, however, it likewise may occur in limited areas, as seen so characteristically in polyps with the typical Swiss cheese pattern. Wherever hyperplasia occurs, however, there is ample evidence, experimental and otherwise, that it is due to estrogenic stimulation. In fact, no other cause has, so far as I know, been suggested by any one, and I therefore do not know what type of "local factors" Dr. Taylor has in mind as causing endometrial hyperplasia. If we were discussing bleeding, such as that seen with some polyps, the question would be a very different one.

Dr. Hofbauer's reference to the underlying role of the pituitary is also in accord with the accepted view of the dominance of this gland over the endocrine function of the ovary. He refers to his results, as yet unconfirmed by others, on a direct proliferative effect of the pituitary on the basal layer of the endometrium. On the other hand, numerous investigators have been able to produce hyperplasia in castrated women or animals by means of adequate estrogenic stimulation, so that there would seem to be no question that estrogen is the immediate factor concerned in the production of this endometrial picture.

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While it is the conviction of the staff that total hysterectomy is the preferable procedure in performing transabdominal hysterectomy, it was found necessary to compromise and resort to supravaginal amputation in 30 per cent of the total number of cases. In explanation of this, we might point out that supravaginal hysterectomy was performed in 188 of the 372 colored cases, as compared with 67 of the 456 white cases. Thus, the ratio of incidence of subtotal hysterectomy to total hysterectomy in the colored and white cases was 3 to 1, respectively. This high ratio of incidence for subtotal hysterectomy in colored women was due to several factors. A large percentage of these colored patients have extensive adhesions and residual exudates resulting from repeated pelvic infections. The fibroids present are not only of multiple type, but are usually of gross dimensions and practically always show extensive degenerative changes. Categorically speaking, the colored woman rarely seeks an explanation for even a protracted menorrhagia, but rather waits for the intervention of pain before consulting a doctor, when the fibroids have become very large, or when adhesions and exudates have become widespread from repeated attacks of salpingitis. Secondary anemias, arteriosclerosis, and myocardial disease, and the high percentage of syphilis, are all factors which render the colored woman less surgically fit for the more radical type of operation. Confronted with extensive adhesions, large fibroids, or similar complicating factors, senior residents, who have been permitted operating privileges without supervision, frequently elect the subtotal in preference to the total operation. A large number of the subtotal operations were performed by them under these circumstances.

For the same reasons, vaginal hysterectomy was elected infrequently in the colored women. Vaginal hysterectomy, a popular procedure on our service, has lost some favor in the last two years because of the frequency of postoperative urinary complications. It is also the conviction of the staff that this procedure, although it can be accomplished in almost any woman, is not satisfactorily performed except where there is beginning prolapse of the uterus and reasonable mobility of this structure. Its performance, as advocated by a few men, in the presence of a fixed uterus, salpingitis, or large fibroids, increases the operating time and the operative trauma, and makes the removal of the uterus, which might have been simple and easy if undertaken abdominally, a time-consuming, bloody, and laborious task, and the end-results under these circumstances are by no means universally desirable.

A study of the comparative frequency of the three types of operation in the colored and the white woman brings out some interesting information (Table II).

These figures evidence the growing popularity of total over subtotal hysterectomy in our service, as there was an increase from 25 per cent total hysterectomies in 1939, to 50 per cent in 1940 in the colored cases, and from 39.6 in 1939 to 51.1 per cent in 1940 among the white cases. This increase in the number of total abdominal operations was not due to a neglect of the vaginal approach, as the percentage of vaginal hysterectomies remained approximately the same for the two

There need be little or no sacrifice of the length of the vaginal canal if care is exercised in severing the vaginal cuff close to its attachment to the cervix. Indeed, the depth of the vagina may be actually increased by dissecting the vaginal mucous membrane loose from the cervix, and, by traction, peeling this layer away from the portio almost to the opening of the external os, before the vaginal canal is invaded.

Dyspareunia is an infrequent complaint following total hysterectomy, in our experience. When it has occurred, it has resulted from limitation of the elasticity of the vaginal vault occasioned by overshortened, and consequently rigid, ligaments being fixed to the vaginal cuff; from an ovary being dragged too deeply into the pelvis and immobilized by an improperly placed suture; from the formation of adhesions between a segment of the small bowel and the operative field; from a failure to peritonize all raw surfaces; or lastly, from an incorrect realignment of perineal supports when vaginal plastics are done coincidentally.

Total abdominal hysterectomy and vaginal hysterectomy are the operations of choice with the gynecologist, but there is no gainsaying the fact that they are surgical procedures of some magnitude and should not be undertaken by a novice. If the experience of the operator is limited and if his knowledge of pelvic anatomy is not absolute, it is far safer for him to elect the supravaginal type of operation, because it is technically more simple, and serious postoperative sequelae are less likely to occur.

Cauterization of the cervix combined with subtotal hysterectomy can never, and should never, replace total abdominal hysterectomy. This statement is based upon the personal observation of several instances in which the combined procedure has been most unsatisfactory. The frequency with which the cervical stump has to be removed, due to a continuation of the patient's complaint, long after supravaginal hysterectomy and combined cauterization and plastic on the cervix have been performed, certainly offers evidence that neither cauterization, repair, nor reconstruction of the cervix can be associated with subtotal hysterectomy as a satisfactory substitute for the total removal of the uterus. The gynecologist who would claim superiority for cauterization of the cervix in association with subtotal hysterectomy admits the fallacy of his logic in the claims which he advances, for certainly, if the cervix is so diseased as to require cauterization, it is far better removed.

The comparative percentages of incidence of the three types of hysterectomy in the total series of 828 cases is summarized in Table I.

TABLE I. INCIDENCE OF VARIOUS TYPES OF HYSTERECTOMY IN 828 CASES

TYPE OF HYSTERECTOMY	NUMBER OF CASES	PERCENTAGE OF INCIDENCE
Total abdominal	374	45.2
Supravaginal	255	30.9
Vaginal	199	23.9

It will be observed that in these 828 cases in which it was thought hysterectomy was indicated, complete removal of the uterus was done abdominally or vaginally in 573 cases, or in 69.1 per cent.

The factor of anesthesia should also be considered in its effect upon mortality, and it may be mentioned that, with the exception of some few cases of spinal anesthesia, all of these patients were anesthetized by graduate nurses who are students in anesthesia. Three of the deaths in the entire series were considered as anesthetic in origin. In addition, another three deaths may be regarded as due to factors not associated with the surgical procedure, since one of these patients died of a proved coronary thrombosis (autopsy) another (a cardiac patient) died forty days postoperatively from acute dilatation of the heart, and the last died six weeks postoperatively from bronchopneumonia and pyelonephritis. No attempt has been made to correct the mortality figures given.

An attempt was made to determine the morbidity rate of these types of hysterectomy, based on the number of hospital stay-days and temperature runs of 100.4° F. for three successive days, not counting the first postoperative day. The number of normal postoperative stay-days was set arbitrarily at fourteen days for total abdominal and vaginal hysterectomies, and at twelve days for supravaginal.

*Total Abdominal Hysterectomy—374 Cases:*

287 cases 76.9% had estimated normal hospital stay-days.

87 cases 23.5% remained longer than estimated normal stay period.

*Supravaginal Hysterectomy—255 Cases:*

164 cases 64% had estimated normal hospital stay-days.

91 cases 36% remained longer than estimated normal stay period.

*Vaginal Hysterectomy—199 Cases:*

143 cases 71.8% had estimated normal hospital stay-days.

56 cases 28.2% remained longer than estimated normal stay period.

Temperature records for the three types of operation were:

*Total Abdominal Hysterectomy—374 Cases:*

296 cases 79.1% had no morbid temperature runs.

78 cases 20.9% had morbid temperature runs.

*Supravaginal Hysterectomy—255 Cases:*

211 cases 82.7% had no morbid temperature runs.

44 cases 17.3% had morbid temperature runs.

*Vaginal Hysterectomy—199 Cases:*

143 cases 71.7% had no morbid temperature runs.

56 cases 28.3% had morbid temperature runs.

Analyzing the specific causes of morbidity in the three types of hysterectomy showed that urinary infection was the prime cause of increased stay-days and temperature elevation, and was present in the following percentages of cases:

Total abdominal hysterectomy	41.3%
Supravaginal hysterectomy	28.5%
Vaginal hysterectomy	69.3%

Wound infection came second with:

Total abdominal hysterectomy	22.6%
Supravaginal hysterectomy	18.6%
Vaginal hysterectomy	13.4%

TABLE II. INCIDENCE OF VARIOUS TYPES OF HYSTERECTOMY IN 456 WHITE AND 372 COLORED WOMEN

TYPE OF HYSTERECTOMY	1939		1940		TOTAL
	CASES	%	CASES	%	
White					
Total abdominal	73	39.6	139	51.1	212
Supravaginal	35	19.0	32	12.1	67
Vaginal	76	41.4	101	36.8	177
	184		272		456
Colored					
Total abdominal	34	25.0	128	50.0	162
Supravaginal	94	61.7	94	39.8	188
Vaginal	8	13.3	14	10.2	22
	136		236		372

years, and the actual number of vaginal hysterectomies performed increased considerably in 1940 as compared to 1939. It is interesting to note that in the entire series of colored patients, vaginal hysterectomy was the type of operation chosen in only 22 cases. The reason for this low incidence has already been commented upon.

The large increase in the total number of hysterectomies performed in 1940, as compared with the total number of hysterectomies performed in 1939, was not due to any widening of the indications for hysterectomy on our part, but was due entirely to the fact that the number of beds in our service had been doubled upon occupation of the new Charity Hospital building.

There were 14 deaths in the series, accounting for a total mortality rate of 1.6 per cent. Dividing these deaths among the three types of hysterectomy, reveals data as to mortality as shown in Table III.

TABLE III. MORTALITY OF VARIOUS TYPES OF HYSTERECTOMY IN 828 CASES

TYPE OF HYSTERECTOMY	NO. OF CASES	NO. OF DEATHS	MORTALITY RATE
Total abdominal	374	5	1.33%
Supravaginal	255	7	2.75%
Vaginal	199	2	1.0 %

I might add parenthetically that the mortality rate for the 1940 series of 267 abdominal operations was 0.75 per cent. This low death rate is due, I believe, to better operating room facilities, better preoperative care, particularly more careful preparation of the vaginal tract, and to improved operative technique.

While the death rate in supravaginal operations has been higher than in total abdominal hysterectomies, it must be taken into consideration that a fair percentage of the subtotal hysterectomies were performed on patients who had extensive pelvic adhesions, and upon patients who, for other reasons, were considered bad risks. The factor of the individual skill of the separate physicians also plays some part, and it would have been interesting to compare the mortality of residents' cases against the mortality of staff cases, etc., but this was not determined.

We were unable to find any reason to feel that an additional plastic procedure added any particular risk to the surgical procedure, or increased the postoperative morbidity beyond some additional discomfort and the necessity for catheterization in a larger number of cases.

Surgery other than hysterectomy was necessary in 30 per cent of colored and 18 per cent of white cases in the total abdominal group, and in 40 per cent of the colored and 12 per cent of the white cases in the subtotal hysterectomy group. Additional operative procedures were salpingectomy, oophorectomy, releasing of adhesions, cauterization of isolated areas of endometriosis, repair of incisional hernias, temporary colostomy, repair of accidental injuries to the bladder. The latter occurred five times in the series. In four cases, the rent in the bladder was closed immediately with complete success. In the fifth case, the left ureter was ligated in doing a complete hysterectomy and a ureterovaginal fistula developed postoperatively. The damaged ureter was recently successfully implanted in the bladder.

Incidental appendectomy was performed in 45 per cent of the total abdominal group, and in 43 per cent of the subtotal group. How many cases had had previous appendectomy was unfortunately overlooked in the preparation of these data. It is our custom to remove the appendix following hysterectomy in all cases except those in which the hysterectomy has been tedious and time consuming; or in which the removal of extensive adnexal pathology has prevented proper peritonealization of all raw surfaces; or where, because of some general condition, the patient was thought to be none too good a surgical risk.

From the foregoing data, we feel justified in submitting the following conclusions:

1. Hysterectomy, regardless of the type, is a comparatively safe surgical procedure when done by the trained specialist.

2. Total hysterectomy is the preferable type of transabdominal approach, because with the removal of the cervix such postoperative sequelae as leucorrhea and chronic foci of infection are removed, and the subsequent hazard of carcinoma of the cervix is eliminated. The mortality in the group of total hysterectomies studied was lower, and the morbidity rate was only slightly higher than those of the subtotal group.

3. Subtotal hysterectomy should be the procedure of election in cases in which the pathology is extensive and necessitates a tedious and time-consuming operative procedure, or if the experience of the surgeon is limited.

4. Vaginal hysterectomy deserves its position of popularity because of its relative safety, the fact that there is less postoperative shock and distention, and because of the excellent end results obtained. We feel, however, that such results are obtained only when the conditions previously mentioned are present, which render the technique of vaginal hysterectomy comparatively simple.

Other causes of morbidity, singly or combined with the above factors, were postoperative vaginal bleeding, thrombophlebitis, postoperative irradiation following operations for carcinoma of the fundus and malignancy of the ovaries, localized peritonitis, diabetes, partial obstruction, hypertension with myocardial disease which required the patients to remain in the service for further care from the medical staff after operation.

How to reduce the high rate of postoperative urinary infections remains a controversial issue. If, when, and how often to catheterize? Should bladder irrigations be resorted to, or should chemotherapy be relied upon entirely? Should retention catheters be inserted, and how long should they remain? All these types of prophylactic and active treatment of urinary infections have their advocates, with about the same ultimate results. It is worthy of note that in the total abdominal and vaginal types of hysterectomy, where the bladder is apt to be traumatized most, the incidence of urinary infection is highest.

It is our impression that this high incidence of urinary infection is due, in some degree, to an overworked nursing staff in a public institution, where the ratio of patients to ward nurses is exceptionally high, and prompt catheterization of the individual patient is almost impossible. Postoperative retention is consequently common. The use of indwelling catheters has decreased the urinary retention, in the cases employed, but has not appreciably altered the incidence of infection. It would seem advisable, in the future, to consider the possibility of urinary infection before operation, rather than immediately afterward. In this light, the bladder of every woman who presents a cystocele is either already infected or predisposed to infection. A series of bladder irrigations preoperatively, rather than postoperatively, would seem advisable, and, in addition, the administration of urotropin and an acidifying agent in appropriate doses for several days preoperatively up to the date of operation would increase the incidence of spontaneous urination due to the increased vesical tone which would result. In several private cases, this procedure has been most satisfactory.

We were surprised to find such a large number of wound infections, but on careful study of the charts it was found that all wounds were classified as infected in which there was any evidence of failure to heal primarily, or in which there was only a slight amount of pus about a retention or skin approximation stitch.

An interesting and gratifying finding was that in the total abdominal and vaginal hysterectomies, twelve cases of very early carcinoma of the cervix were reported as being found in the microscopic survey of the tissues submitted to the Pathological Department. On the other hand, we are not aware of the subsequent development of this lesion on the cervix of any of the cases for whom a supracervical amputation was done.

The number of incidental vaginal plastic operations done in this series were:

Total abdominal hysterectomy	91 cases	10.7%
Supravaginal hysterectomy	56 cases	6.7%
Vaginal hysterectomy	199 cases	100.0%

In 1921 John O. Polak collected 900 cases of total hysterectomy from the clinics of Schottlaender, Herbert Spencer and Noble, among which were found 2 per cent of carcinomas. Since that time the question has been argued at various times. Von Graff in 1934 collected 1,169 cases of carcinoma of the stump of the uterus after subtotal hysterectomy. If this number can be found in the literature or obtained by inquiry directed to known workers in the field of gynecology, the number of cancers after subtotal hysterectomy is sufficiently great to arouse our active interest. It is generally assumed that the incidence of carcinoma in the retained stump is about 2 per cent; Richardson believes the incidence to be 3 per cent. Masson reports that, of 1,489 cases of carcinoma of the cervix seen at the Mayo Clinic, 65, or 4.4 per cent, were stump cancers. Henriksen, who studied 940 cases of cancer at the Johns Hopkins Hospital, found 2.3 per cent of them to be cancers of the retained stump. Behney reported 910 cases of cervical cancer at the University Hospital in Philadelphia and found 43 cases of cancer of the retained stump, or 4.7 per cent. He also reported 1,117 cases of cervical cancer at the Philadelphia General Hospital, of which 24, or 2.15 per cent, were cancers of the stump. Ward saw 61 stump cancers, or 6.9 per cent, of 879 cancers of the cervix.

That carcinoma of the cervical stump is a real danger and that it occurs with a disturbing frequency must be admitted. The surgeon who has not seen such a case in his own practice may feel that this danger is an overrated one but he forgets that many patients, who have trouble after any surgical procedure, are likely to seek advice from some one other than the original operator, who, they may conclude, has not met the situation completely.

TABLE I. INCIDENCE OF STUMP CANCER

	NO. CASES CA. CERVIX	NO. STUMP CA.	PER CENT
Masson	1,489	65	4.4
Henriksen	940		2.3
Behney—Univ. Hosp.	910	43	4.7
Behney—Phila. Gen.	1,117	24	2.15
Ward	879	61	6.9
Total	5,335	193	4.01

In addition to the risk of cancer, the retained stump may be troublesome in other ways. Endocervicitis or cervicitis is prone to develop and many of these women complain of leucorrhea later. The circulation of the cervix is disturbed and it responds poorly to treatment. Polyps sometimes develop and require removal, and troublesome bleeding due to inflammatory damage to the cervix may appear. I have had to remove a number of cervical stumps, some of which were in patients operated upon by me and some of which had been done elsewhere, either because of bleeding or to eliminate a possible source of infection.

The comparative risk of the two operations is often urged in favor of the subtotal operation. It is freely admitted that in the hands of men who do only an occasional hysterectomy the subtotal procedure is to be preferred. Our own experience and the reports in the literature,

## TOTAL HYSTERECTOMY, ABDOMINAL AND VAGINAL\*

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FOR many years the most frequently employed method of removing the myomatous uterus or of excising the uterus for a number of other common causes has been subtotal hysterectomy. The amputation of the uterus is performed at the level of the internal os or below it unless it is desired to leave enough endometrium to cause some loss of blood at the menstrual periods, when the excision is done at a varying level above the internal os. The history of the operation of hysterectomy occupies just less than one hundred years, for it was in 1844 that Attlee removed the uterus for myoma for the first time. The mortality of the operation has steadily decreased as technique has improved and experience has grown until, in good clinics today, it is done with a high degree of safety.

Of late years it has become the practice in some clinics to remove the entire uterus, including the cervix in many and perhaps the majority of cases. Opinions are still divided upon the question of the wisdom of using the more extended operation as a routine procedure and many clinics still make use of supravaginal excision as the usual operation, reserving the total operation for cases in which malignancy is suspected or is known to exist, or for patients whose cervixes are notably unhealthy. The argument in favor of the more extended operation has revolved largely about the question of carcinoma in the retained cervical stump.

For many years my associates and I were quite definitely of the "subtotal school," removing the cervix when operating abdominally only when carcinoma of the corpus was being dealt with or when the cervix was markedly unhealthy. Some years ago we began to make much more use of the vaginal hysterectomy than we had done. As we accumulated a series of vaginal hysterectomies of some size we began to be impressed with the fact that the women who had the entire uterus removed, as it is in the vaginal operation, came back to us far less frequently for treatment of discharges and bleeding from the retained stump than was the case in our patients upon whom the subtotal operation had been done. Not only because of the risk of cancer in the retained stump but also to free our patients from the results of retention of the frequently unhealthy cervix, we began to make much more frequent use of the total excision of the uterus in those patients who are operated upon abdominally.

The debate as to the value of the total operation is not a new one.

\*Read at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.



both the abdominal and the vaginal operations. The morbidity of the total hysterectomies was 33 per cent, that of 744 subtotal operations studied by Smith was 28 per cent, and that of the vaginal series 42.5 per cent. In spite of the fact that there is a little more fever in the total and the vaginal groups it is notable that convalescence is no less smooth than that of the subtotal operation. By whatever route the uterus is extirpated one passes through an area which is not aseptic. The subtotal operation requires the cutting across of the cervix, which, if it be at the level of the internal os or lower, is a bacteria-containing field. A painstaking preparation of the vaginal field is an essential part of the preparation for either the total abdominal or the vaginal operation.

That the elimination of the cervix is a desirable thing is indicated by a survey of the pathologic reports of the cervices removed in 124 cases. Of these the pathologist reported that 61 showed major abnormalities, as marked eversion, endocervicitis or polyps; 32 were unhealthy to a lesser degree but did have endocervicitis and erosion or eversion; 5 had an atresia in some part of the cervical canal, in one a small myoma was found and 25 were relatively normal. At least half of the cervices of women at the age at which some condition exists which causes the surgeon to consider hysterectomy are unhealthy.

Coning out of the cervix has been urged as a means of protecting the patient against the dangers and disadvantages of the retained cervical stump. About 80 per cent of the stump cancers are epidermoid in type. The process of coning out removes only the epithelium of the canal leaving that which is most likely to be dangerous later on. Bleeding is more likely after an operation in which this measure is used. After trying it in a series of cases some years ago I discarded it as an inefficient procedure. The performance of a cervical plastic followed by a subtotal hysterectomy requires a longer period of anesthesia than a total operation and leaves behind a mass of cervical tissue which may still be troublesome.

It has been urged that the removal of the cervix deprives the vagina of support. This statement is based on an erroneous conception of the mechanics of support of the pelvic structures. If the vagina is in real need of support, an operation should be done, preferably from below, which has for one of its objects the correction of this condition. If the pelvic supports are essentially normal, the vagina may be cared for just as is the cervical stump by the use of the supporting structures of the upper pelvic floor. Dyspareunia will not occur if this is not too tightly done and if the ovaries are not fastened to the vaginal vault.

I have operated upon several cases in which subtotal hysterectomy had previously been done and in which the cervical stump came down. In these cases the corpus had been removed for menorrhagia or for a small myoma while nothing was done for co-existent descent. Whether the cervix remains or does not remain, a lack of support must be cared for if it is present.

The shortening of the vagina, which has been urged against the total and the vaginal operation, does not seem to me to be a valid objection. In a considerable series of total abdominal and vaginal operations we have had no complaints of this. It is true that in some cases operated

however, indicate clearly that in the hands of expert pelvic surgeons the two operations are of equal safety. Masson reports a series of 3,149 hysterectomies of which 1,776 were total, 766 subtotal, and 607 vaginal. The mortality of the total operations was 1.2 per cent, of the subtotal 0.9 per cent, and of the vaginal hysterectomy 1.5 per cent. If the total operation is to be advocated for use in the hands of experienced gynecologic surgeons it must be shown that in their hands it carries a risk which is less than that of the later development of cancer in the stump. The figures just given indicate that the difference is far less than the 2 or 3 per cent which is the incidence of the occurrence of carcinoma in the retained stump. I wish to make it clear that in advocating the removal of the entire uterus I do not mean to imply that all cases should be done by the abdominal route. Vaginal hysterectomy accomplishes the object of removing the cervix, and it was the comparative freedom of our patients who had been operated upon by the vaginal route from annoying discharges and bleeding as well as from the risk of later cancer which directed our attention to the total abdominal operation in cases which were unsuited to attack by the vaginal path. Since making use of the total abdominal operation frequently, we have operated upon 150 women by this method with one death, a mortality of 0.66 per cent. The mortality in a series of 744 subtotal hysterectomies was 0.8 per cent.

TABLE II

	NO.	MORTALITY	MORBIDITY
Subtotal	744	0.8 %	28.0%
Total abdominal	150	0.66%	33.0%
Vaginal	425	0	42.5%

We have removed the uterus vaginally, since adopting this procedure as one of our usual methods, 425 times. The discrepancy in the number of the two operations arises from the fact that the total abdominal operation has been used over a far shorter time than the vaginal operation. In a large series studied by Smith 35 per cent of the hysterectomies were vaginal. Both the vaginal operation and the total abdominal one accomplish the elimination of the cervix and that one should be used which best adapts itself to the case in hand.

In a series of 1,200 hysterectomies analyzed in our service by P. H. Smith the entire mortality was 0.5 per cent and all the deaths were in the subtotal group. This may be accounted for by the fact that during much of the time covered by this study we did more subtotals than any other sort of operation and by the further fact that many of the most difficult cases were done by this method. That we have so far not had a death after vaginal hysterectomy we attribute in some measure to good fortune although all possible precautions are observed and the men in the group are all well trained. It should be said that the majority of these patients were private and that the incidence of severe and extensive inflammatory residues is less than in a large charity service. There is no provision for colored patients, those in our out-patient clinic being cared for elsewhere. This has its effect on the mortality of

It is quite true that in the hands of the occasional operator, or in those of the surgeon who does but few hysterectomies, the subtotal operation is to be preferred. Masson estimates the risk of the subtotal operation in the average hospital as about 4 per cent and that of the total one as 6 per cent. The mortality of subtotal hysterectomy in active and well-staffed clinics is much less than this. Fullerton and Faulkner found that there was a definite difference in the mortality in total cases done by the attending staff and those done by the residents. This would indicate that in the hands of the untrained or the partly trained surgeon the danger of the total operation is greater than when it is done by the experienced pelvic surgeon.

Our own experience and the reports which are available in the literature indicate that the experienced pelvic surgeon can do either the total or the subtotal operation with essentially the same risk, and we have found that the vaginal approach provides a safe and excellent means of disposing of the uterus in many cases. The trained gynecologist can easily develop his technique so that he will do the more extended operation with almost equal ease and with but little more expenditure of time. Lengthy operations are far more productive of shock than are those which are more expeditiously carried out. The man who requires over two hours for the performance of a subtotal operation had better not venture into the total field and the vaginal operation, too, may be better left alone. The gynecologist should be able to do any of these and to complete his work, except in an occasional case of great difficulty, in less than an hour. The risk of wounding the ureters in total abdominal operations is not great if one keeps close to the uterus. It is not necessary to expose them in the great majority of cases. Sufficient light, proper exposure, and nontraumatic management of the bladder and the structures about the cervix will enable the operator with an adequate knowledge of pelvic anatomy to work safely and expeditiously.

One point only of technique will be mentioned. When we did total operations only occasionally, as for carcinoma of the corpus, we were accustomed to drain vaginally. This has long since been given up and at present no drains are used in either the abdominal or the vaginal removals of the entire uterus. The drain is unnecessary and it increases the danger of adhesions. A local peritonitis surrounds the point of which it leaves the abdominal cavity and this may cause the adhesion of a loop of bowel. While the operation of removal of the uterus, by any method, causes an area in which bacteria are found to be opened, the pelvic peritoneum cares for such bacteria as may gain entrance to the peritoneal cavity very efficiently so long as they are confined to one area and not spread about. The only cases which require drainage after the removal of the entire uterus are those of vaginal operation for prolapse in which much dissection is done. In these a small strip of rubber tissue lessens the likelihood of hematoma.

It is generally assumed that a carcinoma which appears in the cervical stump within one year after subtotal hysterectomy was already present at the time of the operation. It is probable that this time limit is too short. Within the past year, in a patient operated upon by one of my

upon vaginally for prolapse there is some shortening but a vaginal adequate for all demands upon it will remain after total excision of the uterus both abdominally or vaginally in cases of other types.



Fig. 1.—Unsuspected carcinoma of cervix found after complete hysterectomy.

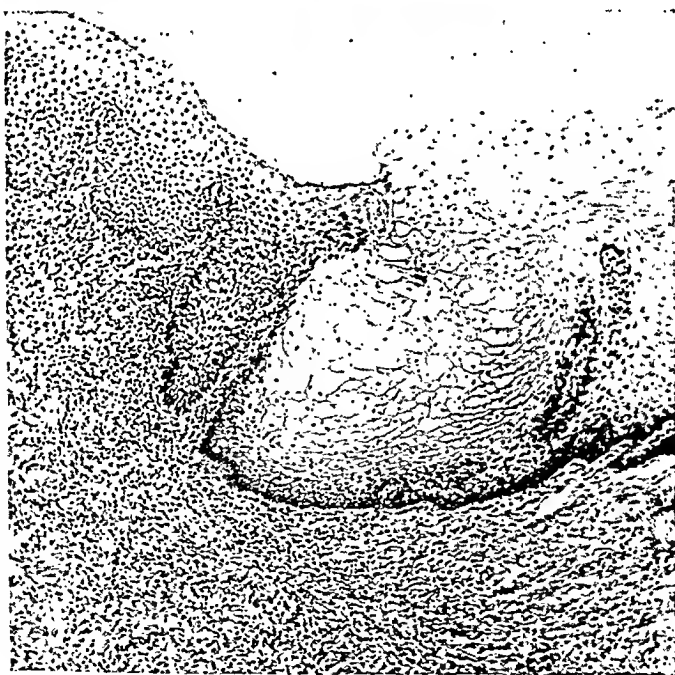


Fig. 2.—Biopsy specimen showing "Schiller's line."

The dryness of the vagina which has been charged against total removal seems also to be infrequent as we have had no patients who have been troubled in this way. If the ovaries are left in a normal condition, with an adequate blood supply, the vaginal mucosa will remain normal.

of the vagina and that the vagina can be just as well suspended as the cervical stump. I also believe that by cutting close to the cervix, especially by using the Richardson technique, the danger of injury to the ureters and bladder is minimal. But I wish to go on record as not favoring the *routine* employment of total hysterectomy. I believe with Dr. Miller that each case should be judged individually, the chief points to be considered being the condition of the cervix, the general condition of the patient, the presence or absence of obesity, and the intrapelvic pathology.

During the past year we have performed approximately 400 abdominal hysterectomies on our service, 74 of which were totals. Over half of these were performed on colored women who are frequently obese and have difficult myomas complicated by salpingitis. We lost one patient by pulmonary embolism, a mortality of a quarter of 1 per cent. There were no deaths among the panhysterectomies. These statistics indicate to me that proper judgment was exercised in choosing the cases for total hysterectomy, for if the operators had insisted upon removal of the cervix in some of the difficult, complicated myomas, I am sure our mortality could not have been held down to such a low figure.

In private practice the conditions are much more favorable to total hysterectomy and I do that operation in approximately half of my cases. However, I still prefer to save the nulliparous and slightly lacerated parous cervices which look healthy and are not the source of leucorrhea, for I believe in the surgical principle that the least amount of surgery to cure the patient is the best.

I think that Dr. Danforth's figure of an incidence of 2 per cent of malignancy in the retained cervical stump is high. This figure *must* be an estimate, for the only way an accurate figure could be obtained would be to follow a large series of women to death upon whom subtotal hysterectomies had been done. I do not believe this has ever been carried out. This figure must of course not be confused with the incidence of stump cancer in cervical carcinoma, which is quite a different thing and surely a much higher figure. In reading Danforth's paper I am a little confused as to just which figures he refers in some of his statistics. I have seen carcinoma develop in only one cervical stump in my private series of subtotal hysterectomies. I do not believe this represents more than one-tenth of 1 per cent of the cervices which I have left in. If a cervix is carefully inspected and biopsied when indicated before a decision is made to remove or retain it, the incidence of carcinoma can be held down to this figure.

Dr. Danforth makes the statement that "the man who requires over two hours for the performance of a subtotal operation had better not venture into the total field." With this I heartily agree but should like to broaden the statement in this way, "the man who requires over two hours for the performance of an average subtotal hysterectomy had better not venture into the field of pelvic surgery."

DR. N. SPROAT HEANEY, CHICAGO, ILL.—I have for years favored the complete removal of the uterus to the supravaginal operation for most of the patients coming under my attention. Earlier I left in more cervices than I do now. When I learned by experience how resistant to treatment an infection is, which occurs in the atrophied cervix left after a supravaginal hysterectomy, I left fewer and fewer cervices to annoy me and the patients in after years. Though in 100 cases of cancer of the cervix two or more may be in a cervical stump, this does not in any way mean that carcinoma occurs in 2 per cent of the cervical stumps left after 100 supravaginal hysterectomies. However small this incidence is, it is a danger avoided by the complete removal of the cervix.

Dr. Miller speaks of the cervix acting as a focus of infection for the production of an arthritis or other disease. I was raised in the institution which put focal infections "on the map." I am firmly convinced of the role of focal infections in the teeth and tonsils in the causation of affections in distant organs. Though I have had the question of the cervix in this regard constantly in my mind through all these years, I have yet to see a proved case. That a cervix, the seat of an acute gonorrhea, may cause gonorrheal rheumatism is true without question. I have also seen arthritis develop immediately after the intrauterine administration of radium and have seen the arthritis cured by the removal of the uterus with

associates for small fibroids and menorrhagia, a very small clinically unrecognized carcinoma was found. A study of cervixes of cases dealt with by the removal of the entire uterus disclosed many which were definitely abnormal. Whatever the relationship of these changes to cancer, it may at least be said that an unhealthy structure has been done away with. Some of these show an epithelial activity, which, while not cancerous, at least indicates an activity which is not normal.

It is notable that we have had no cases of embolism and phlebitis after vaginal hysterectomy and I believe that in two other well-known gynecologic services, in each of which a large number of vaginal hysterectomies have been done, no embolism or phlebitis has appeared. Should continued experience in a number of clinics bear out this observation it may well be regarded as an added reason for the employment of this procedure.

In about 3 per cent of myomatous uteri coincident adenocarcinoma may be found. As more hysterectomies are done for myomas than for any other single reason the removal of the entire uterus is wise unless the carrying out of the total operation subjects the woman to a risk greater than the incidence of cancer. This, in experienced hands, will not be so.

The complete removal of the uterus, abdominally or vaginally, for many benign conditions as well as for carcinoma of the corpus, should be done more frequently by experienced pelvic surgeons, inasmuch as, in their hands, the patient runs no added risk. In institutions in which but little gynecologic surgery is done, the subtotal operation will be safer.

#### CONCLUSIONS

1. To avoid the danger of cancer in the retained stump and to free the patient from the annoyance which may be caused by the unhealthy stump, a wider use of the total removal of the uterus is recommended.

2. Total hysterectomy may be done either abdominally or vaginally, as the conditions of the individual case may suggest.

3. The gynecologic specialist should be able to remove the uterus either abdominally or vaginally with sufficient ease that his choice of operation is not influenced by his lack of experience with one or the other nor should he choose the incomplete operation instead of either because he feels that he can do it more easily.

4. Technique of either of these operations may be developed by the experienced operator.

5. The objections which have been urged against the complete removal of the uterus disappear if a proper technique is used.

6. Total removal in experienced hands, either abdominally or vaginally, does not subject the patient to increased risk.

7. The operator of small experience in pelvic surgery should make use of the subtotal operation.

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#### DISCUSSION ON PAPERS BY DR. MILLER AND DR. DANFORTH

DR. RICHARD W. TELINDE, BALTIMORE, MD.—I believe that total hysterectomy should be done more frequently than it has been done in the past. I believe that if done by the proper technique it can be done without appreciable shortening

There were 49 subtotal hysterectomies, with one death. In this case the woman weighed 260 pounds, had a huge ventral hernia and also multiple fibroids in the uterus. It was thought advisable to remove the uterus to help make room for the multiple coils of intestine that had been outside the abdomen for many years and replacing them markedly raised the intra-abdominal pressure.

I am absolutely in accord with both of the essayists that any one who is doing much pelvic surgery is keeping the best interest of the patient in mind by removing the cervix in most cases. It has not been at all uncommon in my experience to see a woman in the Clinic some time after a subtotal operation with a history of having had no leucorrhea until after the operation. Practically all of these patients are suspicious of cancer with a development of this kind.

The danger of cancer in the cervical stump, even if the number of cases is small, is appreciated by all. In the Clinic to date we have seen altogether 193 cases of cancer of the cervical stump left after subtotal abdominal hysterectomies, and we have seen about four times that many cases with cervicitis. In about 50 per cent of these cases, excision of the cervical stump was advised.

I agree with both essayists that until a satisfactory technique for the total abdominal hysterectomy is arrived at, the subtotal operation is a safer one, but I think that the Members of the Gynecological Society should be the ones to draw special attention to the fact that many of the subtotal operations which are being done today are not entirely satisfactory. My own experience is that thrombophlebitis, pulmonary embolism and other causes for morbidity and mortality are definitely higher following the subtotal operation. I think that this is due to the fact that an infection often results from cutting across infected glands in the cervix causing low-grade retroperitoneal inflammation with resulting thrombophlebitis or the development of a small abscess. This is especially true if hemostasis is not perfect in the operative field.

I agree with both Dr. Miller and Dr. Danforth that prolapse of the vaginal vault, shortening of the vagina and dyspareunia should not be charged to a total hysterectomy because all these conditions are due to faulty technique or failure to do satisfactory vaginal plastics at the same time.

One interesting point, that was suggested by my secretary, is that in my earlier experience, when I did a great many subtotals, the correspondence and repeated examinations were much more frequent than they are at the present time. In fact, there is no group of patients that seem so well satisfied and require so little care following surgery as those in which I have done total hysterectomies.

Among the subtotal hysterectomies that I am reporting there is one death two years later as a result of an obstruction. I operated upon another patient, fifteen years after she had had a pelvic operation elsewhere, in whom a loop of small bowel had become adhered in the pelvis. Just how many patients have obstruction or subacute obstruction or enough adhesions to have occasional gas pains, it would be hard to estimate. There is no doubt that many of the patients who have trouble following surgery in one hospital will go to another, or to another surgeon if they have complications. I am satisfied that following the subtotal operation, the leaving of an infected cervix, especially if the infected glands have been cut through, make a low-grade pelvic peritonitis much more likely, and adhesions are likely to form as a result.

Conization or cauterization after the subtotal operation is not a satisfactory protection against later malignancy and probably predisposes to local infection, as we leave a raw surface exposed to infection from the vaginal canal. When we consider that this is just beneath the peritoneum, it is reasonable to believe that there is often a little local peritonitis which would account for many of the adhesions deep in the pelvis.

DR. SIDNEY A. CHALFANT, PITTSBURGH, PA.—In the Pittsburgh hospitals for many years, it has been the practice to do the supravaginal hysterectomy in the great majority of cases. This, with the thorough cauterization of the cervix has been almost the routine procedure. At present Dr. Cashman has in process a study of all patients who have had a previous cauterization at Magee Hospital to determine the incidence of cancer after this procedure.

its contained infected radium ulcer. With these two exceptions, I have never seen the cervix or the uterine body act as a focus of infection in the etiology of disease at a distance.

If the cervix requires any surgical attention at the time the uterus is to be removed, then the cervix should be removed at the same time. I believe that the cervix should never be cauterized either from above or from below at the time of the removal of the uterine body. The burning is too liable to cause a latent infection to become acute.

To my mind a conization should never be done either on the intact uterus or upon the uterine stump. This procedure should be completely eliminated from our list of operative resources.

It has been said that a vaginal hysterectomy leaves a shortened vagina. If the incision in the vagina is made at the same level as it would be made if doing a complete abdominal hysterectomy, then I cannot see why the route by which the uterus is removed can influence the length of the vagina. When a vaginal hysterectomy is done as part of the cure of a complete prolapse, then the vagina will be found to be short after the operation, for it was short before the operation, since a part of its length had been used in making up the breadth of the prolapse.

Since the attachments of the bladder to the uterus are the same whether the uterus is to be removed completely, vaginally, or abdominally, I cannot see why bladder difficulties should be commoner after vaginal hysterectomy than after abdominal hysterectomy, if the same perfection of technique is exercised.

From time to time I encounter a case where a combined abdominal and vaginal hysterectomy seems to be indicated. Where a cervix is very large, extensively torn or badly infected and the uterine body is too fixed to venture a vaginal hysterectomy, the cervix may be thoroughly cauterized and then removed as high as the uterine vessels. The vaginal vault may then be closed, a perineal repair, if needed, be done, and the abdomen entered for removal of the rest of the uterus. Where the pelvic tumor is so shaped or situated as to make the uterine vessels difficult of access from above, the combined operation may be done to very great advantage.

Since using ethylene gas, I have now completed 991 vaginal hysterectomies for benign disease of the uterus, with the same three deaths which have been previously reported in detail, with a mortality rate of approximately one-third of 1 per cent. I wish to congratulate Dr. Danforth on his having had no deaths in his series of 425 cases. I, too, have done almost 400 cases since my last fatal case.

Dr. Miller states that "although vaginal hysterectomy may be accomplished in almost any woman, it is not satisfactorily performed except where there is beginning prolapse of the uterus and a reasonable mobility of the structures." In the last 100 cases that I have done, the uterus was so large in 53 women that it had to be cut into two or more pieces to remove it. On the contrary, the uterus may be most easily removed in a nulliparous woman provided the vagina is not too tight, particularly if the vaginal vault is of normal proportions. If there is a little too much laxity of the vaginal walls they may fall together laterally and obscure the operative field. The easiest vaginal hysterectomy I ever did was on a 45-year-old virgin with an intact hymen and a small uterus full of tiny fibroids. A median incision of the hymen was made and the whole operation proceeded with the greatest of ease. There were 269 women in my series who were nulliparas.

DR. JAMES C. MASSON, ROCHESTER, MINN.—This subject is one in which I have been much interested for many years. In the five-year period from 1935 to 1939, inclusive, I have performed 1,277 hysterectomies. Of these, 888 were total hysterectomies with 6 deaths or a mortality rate of 0.67 per cent. One of these deaths should really not be charged to the hysterectomy, as the operation was done for tuboovarian abscesses and an apparently normal uterus was simply removed on account of the raw surface left after freeing up the inflammatory condition. Another death was due to pulmonary embolism. A third patient was a hunchback who died of atelectasis shortly after the operation.

In the series were 340 vaginal hysterectomies with one death. The probability is that this patient died of a ruptured appendix rather than anything resulting from the operation, but autopsy was refused.



As to the statistics to which Dr. TeLinde referred, I think that he made a valid objection. The 2 per cent given by writers in the literature referred to the incidence of carcinoma of the stump in relation to all such stumps left in after the subtotal procedure. The larger figure merely indicates the percentage of carcinomas found in the retained stump in relation to all the cervical cancers seen in other clinics.

In my experience, after the usual type of vaginal hysterectomy which is done for nonmalignant bleeding or for small fibroids, the bladder usually gives little trouble. It is usual to have the woman urinating by the second day.

The question of carcinoma has been stressed rather unduly, to the neglect of the other conditions. Carcinoma of the stump does appear in some women but when the cervix becomes infected it is difficult to manage.

One point should be remembered about burns in extensive cauterization. A burn is the slowest healing type of wound there is. I have never been enthusiastic about cauterization of any type except the conservative cauterization which one does for the relief of leucorrhea. I have never been enthusiastic about cauterization at the time of operation.

At Magee Hospital during the six years ending June, 1940, there were 976 hysterectomies by all operators with 18 deaths, or 1.84 per cent. The supravaginal operations predominated greatly, 874, with 14 deaths, or 1.6 per cent. The total abdominal hysterectomies numbered 54 with 2 deaths (3.73%); the vaginal hysterectomies, 48 with 2 deaths (4.17 per cent). The total abdominal operations were practically limited to cases of carcinoma of the fundus. During the same time on my personal service, there were 102 supravaginal operations with 1 death from peritonitis, and 6 total and 5 vaginal operations without mortality.

It is admitted that a competent gynecologist should be able to do the complete operation in the average case with no greater mortality or morbidity than the supravaginal operation. But there are many patients requiring hysterectomy in whom it is either (1) not necessary to do the complete operation, or (2) in whom it is more difficult and more dangerous.

The first class would include the fibroid case in the virgin who has no erosion of the cervix and who has had no opportunity for infection. There should be no postoperative leucorrhea as there has been none before the operation, and the incidence of cancer of the cervix in the nullipara is slight.

In the difficult class we would include particularly the fibroids associated with old inflammatory disease, where the uterus is firmly fixed in the pelvis and the dissection difficult. Here we do a thorough cauterization of the cervix and a supravaginal hysterectomy. The cauterization of the cervix must be sufficient to destroy all the epithelium in the canal and all the deep glands. Where this is done there is nothing left except a ring of fibrous tissue, the patient is free from leucorrhea, the vagina is not shortened, and the support adequate. There should be no more danger of developing carcinoma of the cervix than there is of a primary carcinoma of the vagina.

It is quite possible that we have been doing too few complete operations. But I am confident that in certain cases the incomplete operation is the safer procedure for the experienced gynecologist as well as for the occasional operator. Those who favor the complete operation are usually able to report just as good or *better* results from this as from the supravaginal hysterectomy. Is it possible that the latter group includes a larger percentage of the complicated cases in which one would naturally expect a greater mortality?

DR. LEWIS C. SCHEFFEY, PHILADELPHIA, PA.—I feel, as Dr. TeLinde and Dr. Chalfant do, that complete hysterectomy should not be routine for all cases. At Jefferson Hospital in Philadelphia we have followed a plan of thorough preliminary inspection of the cervix, and we cauterize nearly every case unless there is an absolutely intact cervix or when excessive hypertrophy, laceration, and eversion make complete hysterectomy seem more desirable.

About five years ago we followed up over 500 cases in which the cervix had been given proper attention and in those cases where that had not been done. Our incidence of carcinoma of the stump in these two groups was 0.5 per cent and 1.0 per cent, respectively. In about 400 cases of cervical carcinoma we have treated 18 cases of stump carcinoma, an incidence of 4.7 per cent. Our present feeling is that in women under 40 years there is a decided advantage in retaining the cervical stump in a healthy condition, or one which has been made healthy by cauterization, especially if it has been possible to conserve one or both ovaries. If we are dealing with a markedly diseased cervix and the patient is approaching, or is at the menopause or beyond it, then we believe in complete hysterectomy.

In certain instances complicating pelvic pathology and a debilitated patient make the complete operation much more hazardous than the subtotal procedure. To our mind, then, the question is not whether or not one is technically able to perform complete hysterectomy, but which procedure is better for the particular patient under consideration.

DR. DANFORTH (closing).—I would like to say in reply to Dr. TeLinde's remarks that I agree entirely with what he said about choosing the operation. Just before leaving home I did two subtotals, one on a virgin of 40 years who had an enormous fibroid and a perfectly healthy cervix. In the second case there was an involvement of the bowel in a bilateral carcinoma of the ovary, and I saw no reason for excising the cervix.

pigments closely resembling those obtained with crystalline hormones. This degree of purification is achieved without incurring serious losses of hormone. The method in its present form, however, is applicable only to pregnancy urine, wherein the ratio of impurities to estrogens is relatively low.

In the procedure, estriol is separated from the other estrogens and assayed directly. Since it is not feasible to effect a similar separation of the remaining estrogens, i.e., estrone and estradiol, without unduly complicating the procedure, these hormones are separated as a combined fraction and the latter then analyzed in the following manner: The sum of the two estrogens is determined by examining one aliquot of the fraction with the Kober reaction. A second aliquot is assayed with the ketosteroid reaction of Zimmermann.<sup>24, 25</sup> Since estrone, in contrast to estradiol, possesses a carbonyl group, this test should indicate the estrone content of our fractions. The difference between the two results is taken to represent the estradiol content. This obviously is based on the assumption that no additional unknown estrogen is present in these fractions.

With the use of these techniques, the estriol and estrone of pregnancy urine can be estimated within limits of error probably not exceeding 10 per cent. The indirect method employed for estimating estradiol involves larger errors, and only fair approximations of the quantities of this hormone are therefore obtainable. For estriol and estrone, however, the accuracy of the method exceeds, we believe, that of the biologic technique of assay. Moreover, the colorimetric technique is far less time-consuming, since it furnishes a complete quantitative assay of the urinary estrogens within two working days.

*Pregnanediol Determinations.*—Pregnanediol was determined by two methods: In one procedure, the technique of Venning and Browne<sup>18</sup> for the isolation of pregnanediol glucuronide from unhydrolyzed urine was employed; the values thus obtained were multiplied by the factor 0.618 to permit their expression in terms of the free steroid. In the second procedure the recently proposed technique of Astwood and Jones<sup>26</sup> for the direct isolation of free pregnanediol from hydrolyzed urine was employed. Although there was a very satisfactory parallelism between the results obtained with the two methods, the values yielded by Astwood and Jones' method were consistently 20 to 40 per cent lower than those secured with the technique of Venning and Browne, the degrees of difference varying among the several patients but showing a characteristic constancy for each patient. Comparison of the results of recovery experiments with both procedures<sup>15, 18, 26</sup> indicates that the discrepancies are largely due to losses entailed in the hydrolysis necessary in the Astwood procedure. We, therefore, believe that the Venning procedure reflects more closely the total pregnanediol of the urine, provided no free steroid is present.\*

\*The nonhydrolyzed urine specimens, as used for the glucuronide determinations, were periodically examined by Astwood's technique in order to determine whether any free pregnanediol was present. None, however, was found. We interpret this as evidence that the urine specimens were well preserved, and that the values obtained with the Venning procedure reflected the total amounts of preformed pregnanediol present.

## THE EXCRETION OF ESTROGEN AND PREGNANEDIOL PRECEDING NORMAL PARTURITION\*

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EVIDENCE supplied by animal experiments indicates that progesterone and estrogenic hormones play important roles in maintaining gestation, and probably also in determining the natural onset of labor.† It would seem reasonable to expect, therefore, that during the prepartal period significant fluctuations would occur in the urinary excretion of these hormones or their metabolic end-products. The data available from studies that have been made to date, however, are not entirely consistent; while they are in good agreement with respect to a few general features, no characteristic fluctuations or critical excretion-levels presaging the imminent approach of labor have been definitely established.<sup>2-17</sup>

Unfortunately, when these studies were made, not all of the methods of assay that were then available were sufficiently accurate to permit the demonstration of small but possibly significant fluctuations of excretion. While pregnanediol glucuronidate could be determined with reasonable accuracy by means of Venning and Browne's isolation procedure,<sup>18</sup> no equally reliable techniques of estrogen assay were at hand. Since fairly accurate colorimetric methods of assaying urinary estrogens have recently been developed in our laboratory, we have been interested in applying them to a further study of this problem. The present communication deals with the data obtained from a group of six patients.

### METHODS

The patients selected for study were healthy young women of average physique and body weight. With one exception they were primigravidas. Their labors were spontaneous in onset and normal in character. Twenty-four-hour collections of urine were obtained from each patient twice weekly during the last three to nine weeks of gestation. These were analyzed for their content of estriol, estrone, estradiol, and pregnanediol.

*Estrogen Determinations.*—Our colorimetric procedure for the estimation of urinary estrogens has been described in detail elsewhere.<sup>19</sup> It is based upon the use of Kober's phenolsulfonic acid reagent, with which the natural estrogens form a characteristic pink color. The procedure differs from previously proposed colorimetric techniques<sup>20-23</sup> in that the urinary estrogens are purified sufficiently to yield with the color reagent

\*Read by invitation, at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

†The experimental literature, and the clinical implications thereof, have been admirably summarized by Reynolds.<sup>1</sup>

excretion of the different hormones were either constant or changed very gradually; it would be impossible, therefore, to forecast from either a single day's determinations, or from a series of consecutive determinations, the date on which labor would begin.

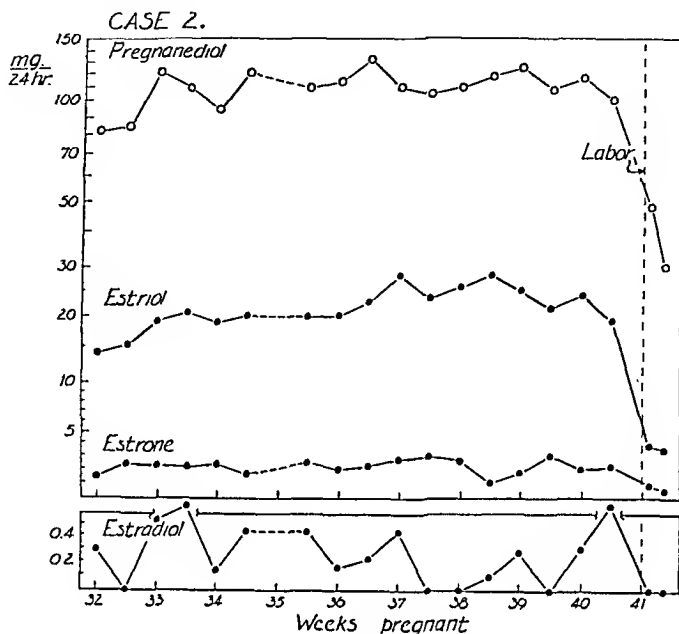


Fig. 2.—Urinary hormonal excretions during the last nine weeks of gestation, and the first two post-partum days, in Case 2.

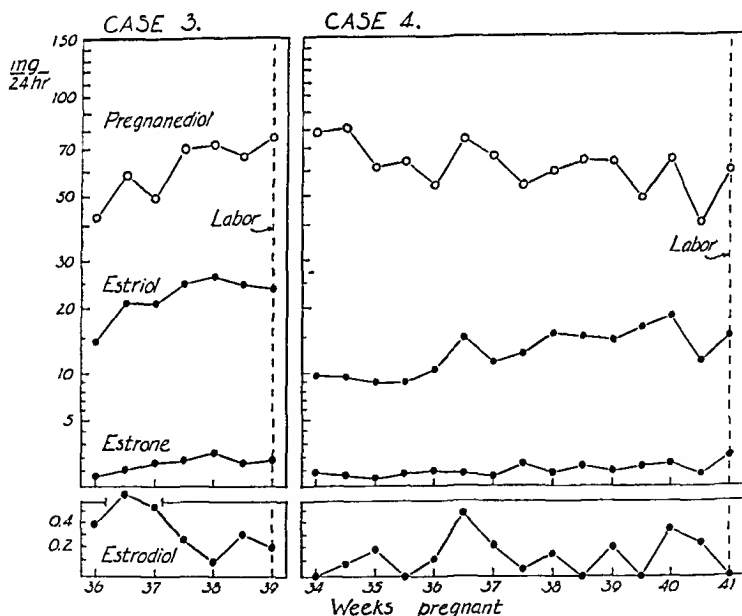


Fig. 3.—Urinary hormonal excretions in Cases 3 and 4. In these patients, the final urine samples were obtained within a few hours of the onset of labor.

CASE 2.—Fig. 2 summarizes the results obtained in this patient, a 20-year-old primigravida, who delivered a 3,000 Gm. fetus at the forty-first week, following a labor of sixteen hours' duration. The continuous curves of excretion in her record are not as smooth as in that of the previous patient. However, the levels and trends of all of the hormonal excretions shown in this figure resemble in a general way

*Tabulation of Data.*—Our findings have been recorded on charts, each of which summarizes the observations made upon an individual patient. The abscissas indicate the weeks of gestation during which the urine was examined and the maturity of pregnancy at the time labor began. Ordinates indicate the urinary output, in milligrams per twenty-four hours, of pregnanediol, estriol, estrone, and estradiol on the occasions indicated. In order to illustrate the widely varying amounts of the excretion of these substances with the use of a single scale of measurement, a logarithmic scale has been employed for the ordinate.

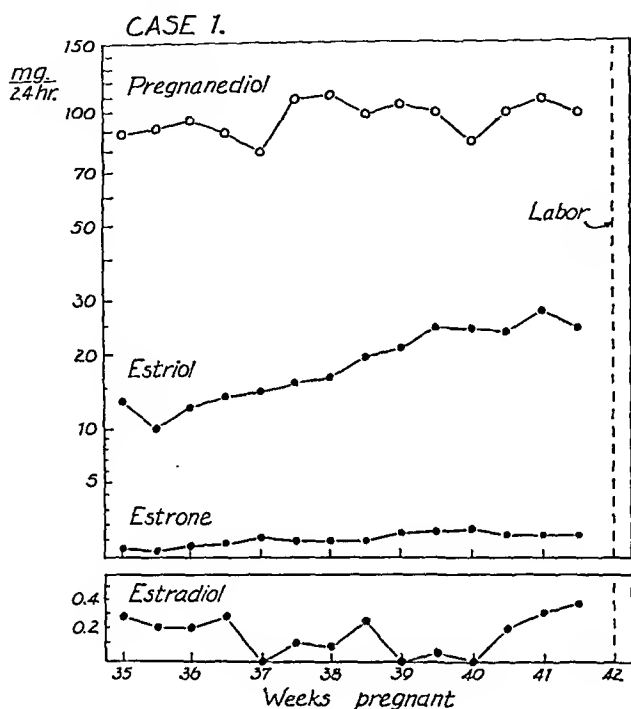


Fig. 1.—Urinary excretion of pregnanediol, estriol, estrone, and estradiol preceding parturition in Case 1. Excretions sampled at twice-weekly intervals during the last seven weeks of gestation. For interpretation of the data in this and the following figures, see the case protocols.

#### OBSERVATIONS

CASE 1.—Fig. 1 illustrates the excretion record of a secundigravida, aged 32 years, who gave birth to a 3,200 Gm. infant at the forty-second week of gestation following a labor lasting five hours. An outstanding feature of her record is the smooth character of the excretion-curves of estriol and estrone. The daily output of estriol rose steadily from a low point of about 10 mg. at the thirty-fifth week to a peak of 25 mg. just before labor. A rise in output of estrone ran parallel to this, though the peak of the daily excretion of this substance was less than 2 mg. The data relative to estradiol cannot readily be summarized; the unavoidable errors involved in the estimation of the extremely small excretions of this hormone undoubtedly account for some of the fluctuations seen in the figure, and permit us to say only that the hormone was present in the urine in appreciable amounts in the days immediately preceding labor. A daily average of about 100 mg. of pregnanediol was excreted during the last seven weeks of gestation; there was a slight upward tendency as term approached, with a peak level occurring at about the thirty-eighth week; temporary but probably significantly low levels were encountered at the thirty-seventh and fortieth weeks. It can be seen that any pre-labor trends in the

remaining patients, and the excretion trends so unique, that we have been at a loss to account for them except on the basis of her very mild medical disorder. Should further work justify such an interpretation, it would indicate that even minor medical disorders accompanying gestation may influence hormonal excretions profoundly.

#### COMMENT

The findings in this small series of patients corroborate, in a general manner, the results of the similar studies of Hain,<sup>8, 9, 12</sup> wherein the estrogens were estimated with biologic methods of assay. They indicate, apart from a pre-labor rise in excretion of estrogens, no constantly discernible correlations between hormonal excretion and the onset and course of normal parturition. Our experience is too limited to permit us to comment upon the observation made by several earlier workers<sup>3, 6</sup> that the rise in estrogen excretion which occurs during gestation is marked by transient cyclic fluctuations; it should be noted, however, that the cases we have so far investigated fail to show such fluctuations. It has been stated that estriol and estrone excretions fall off in amount just before labor begins, whereas the output of estradiol rises at that time;<sup>3, 6, 11</sup> our data offer some support for this suggestion. The observation of several workers that labor is preceded by a rise in the proportion of unconjugated urinary estrogens<sup>2, 11</sup> has not been investigated. With respect to pregnanediol, the data of the present study show no constancy; the pre-labor fall in output of this substance which we found in earlier investigations of both normal and toxemic patients<sup>15-17</sup> was not confirmed in the present series of patients. This clearly demonstrates that further work is necessary on both normal and abnormal patients before definite conclusions can be reached.\* On the other hand, it seems clear at the moment that such studies are not likely to reveal sudden shifts in the prepartal excretions, or to show critical prepartal values, from either of which the clinician may hope to forecast the date or character of the oncoming labor.

Failure to demonstrate marked or sudden changes in hormonal excretion patterns at the end of gestation does not necessarily indicate that the hormones are not concerned in the processes which determine the onset and nature of labor. Currently available methods of investigation may fail to reveal the true nature of these excretion patterns, or the patterns may not reflect the rates of internal secretion and utilization of the hormones.

From the technical standpoint it may be said that it is not possible to effect complete hydrolysis of the conjugated estrogens of urine without causing their partial destruction. The hydrolysis procedures that have so far been proposed<sup>27, 28</sup> represent a compromise that gives optimal results with respect to total estrogen rather than to any individual substance. Although it is probable that future work in this direction will not materially alter the results obtained with present methods, such a study nevertheless seems desirable. Our convenient method of estrogen assay renders the prosecution of such a study more feasible than has heretofore been the case.

\*The present series of patients forms the nucleus of a larger group now being studied in collaboration with Dr. Douglas Murphy, who is investigating the coincidental patterns of uterine motility in these patients with the use of the tocograph.

those exhibited in Fig. 1. There was a higher daily output of estrone than in the first patient. It is noteworthy that the patient excreted relatively large amounts of pregnanediol as late as twenty-four hours following her delivery.

CASE 3.—This patient (see Fig. 3) was a 19-year-old primigravida who delivered a 3,100 Gm. infant at the thirty-ninth week, following a five-hour labor. Her excretion data resemble those of the first two patients, except that the output of pregnanediol was rising rather sharply when labor began, and the estradiol values were at a low level at that point.

CASE 4.—The data of this patient, also illustrated in Fig. 3, reveal further individual variations. This patient was a 17-year-old primigravida who delivered a 3,200 Gm. fetus at the forty-first week of gestation after a labor of nine hours' duration. While the trends and levels of the excretion of the estrogens were, in general, the same as those of the preceding patients, the trend of pregnanediol excretion was slowly downward during the last seven weeks of her pregnancy.

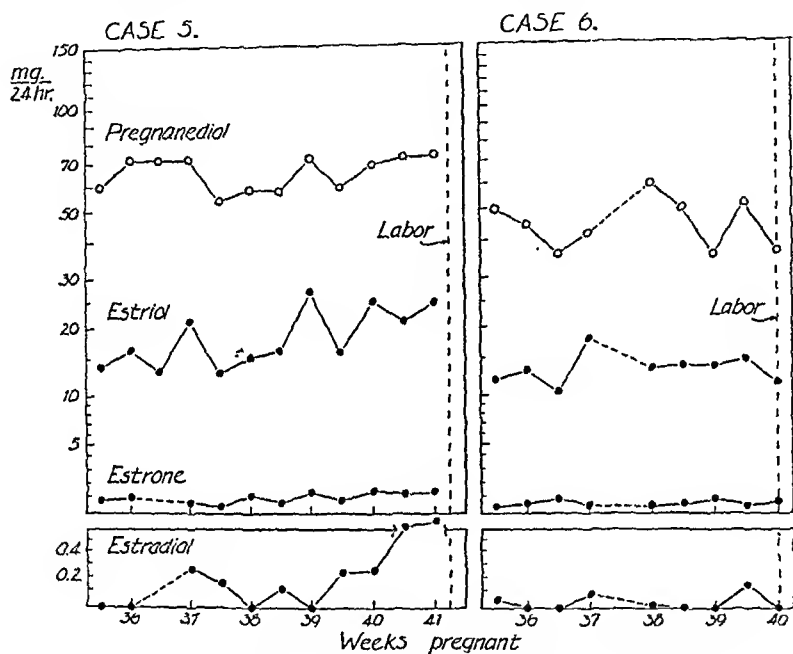


Fig. 4.—Urinary hormonal excretions in Cases 5 and 6.

CASE 5.—This patient was a 20-year-old primigravida who gave birth to a 3,100 Gm. infant at the forty-first week, following a thirteen-hour labor. Her record, illustrated in Fig. 4, may be viewed as an illustration of the difficulties of interpretation sometimes encountered in this type of investigation. It will be noted that while there is a general resemblance between her data and those of the first two patients, the excretion values obtained on successive occasions often varied markedly and without recognizable pattern. Since the values of all of the excreted products frequently fluctuated in the same direction, and tended to deviate with the volumes of the twenty-four-hour urine samples, we suspect that the patient was not always successful in obtaining accurate collections of her urine. Her record, however, shows a striking and unmistakable rise in output of estradiol in the four days preceding the onset of labor.

CASE 6.—This patient (see Fig. 4) was a 26-year-old primigravida, who gave birth to a 3,200 Gm. infant at the fortieth week after a labor of twelve hours' duration. Her health was normal throughout pregnancy except for a very unstable blood pressure, which tended to rise on frequent occasions to moderate hypertensive levels. Her hormonal excretions were so markedly below those of the



- Bachman, C., Leekley, D., and Hirschmann, H.*: J. Clin. Investigation 19: 801, 1940. (16) *Bachman, C., Leekley, D., and Winter, B.*: J. Clin. Endocrinol. 1: 142, 1941. (17) *Bachman, C., Leekley, D., and Hirschmann, H.*: J. Clin. Endocrinol. 1: 206, 1941. (18) *Venning, E. H., and Browne, J. S. L.*: Proc. Soc. Exper. Biol. & Med. 34: 792, 1936; *Venning, E. H.*: J. Biol. Chem. 119: 473, 1937; *Venning, E. H.*: J. Biol. Chem. 126: 595, 1938. (19) *Bachman, C., and Pettit, D. S.*: J. Biol. Chem. 138: 689, 1941. (20) *Cohen, S. L., and Marrian, G. F.*: Biochem. J. 28: 1603, 1934. (21) *Venning, E. H., Evelyn, K. A., Harkness, E. V., and Browne, J. S. L.*: J. Biol. Chem. 120: 225, 1937. (22) *Kober, S.*: Biochem. J. 32: 352, 1938. (23) *Talbot, N. B., Wolfe, J. K., MacLachlan, E. A., Karush, F., and Butler, A. M.*: J. Biol. Chem. 134: 319, 1940. (24) *Zimmermann, W.*: Ztschr. Physiol. Chem. 233: 257, 1935. (25) *Callow, N. H., Callow, R. K., and Emmens, C. W.*: Biochem. J. 32: 1312, 1938. (26) *Astwood, E. B., and Jones, G. E. S.*: J. Biol. Chem. 137: 397, 1941. (27) *Cohen, S. L., and Marrian, G. F.*: Biochem. J. 29: 1577, 1935. (28) *Smith, G. V. S., and Smith, O. W.*: Am. J. Physiol. 112: 340, 1935; Proc. Soc. Exper. Biol. & Med. 36: 461, 1937; *Smith, O. W., Smith, G. V. S., and Schiller, S.*: Endocrinology 25: 509, 1939; *Smith, O. W., and Smith, G. V. S.*: Ibid. 28: 740, 1941. (29) *Dingemanse, E., and Laqueur, E.*: Nederl. tijdschr. v. geneesk. 84: 3287, 1940.

From the theoretical standpoint many explanations might be cited to show why urinary excretions may not reflect the quantitative aspects of the metabolism of hormones. The amounts of any hormonal excretion product recoverable from urine following the experimental administration of the parent substance represent, even under optimal conditions, only minor fractions of the quantities administered. Dingemans and Laqueur<sup>29</sup> have shown that as much as 50 per cent of the total estrogen excreted under certain conditions may be put out in the feces. Also involved in this problem are questions of the sites and rates of utilization and destruction of the hormones, and the efficiency of conjugating and excretory mechanisms in the liver and kidneys. For the elucidation of many of these questions, the new colorimetric technique of estrogen assay should prove useful.

#### SUMMARY AND CONCLUSIONS

Frequent sampling of the urinary excretions of estrogen and pregnanediol during the last weeks of pregnancy was carried out in six healthy women, in order to determine whether any relations could be demonstrated between these excretions and the onset and character of the patients' labors. New and accurate colorimetric methods were employed for the estrogen analyses.

Apart from a gradual rise in output of estriol and estrone as term was approached, no constant patterns of hormonal excretion were observed. The rises in estrogen output were too gradual and the individual variations in the peak levels attained by different patients too marked, to make possible any forecast of the date on which labor would begin. Moreover, the variations in the maximal amounts of the hormones daily excreted by different patients did not appear to relate themselves to such clinical variables as the lengths of the labors or the weights of the infants and placentas.

Although further work is necessary, it appears that the roles which the estrogenic hormones and progesterone may play in the processes of parturition are hardly likely to be demonstrated by the rates at which these hormones or their metabolic end-products are excreted before parturition.

The author wishes to acknowledge his indebtedness and to express his thanks to his associates in the laboratory, Mrs. Dorothy Seymour Pettit and Mrs. Dorothy Leekley, for their valuable assistance in this investigation.

#### REFERENCES

- (1) *Reynolds, S. R. M.*: Physiology of the Uterus, With Clinical Correlations, New York, 1939, Paul B. Hoeber, Inc.
- (2) *Cohen, S. L., Marrian, G. F., and Watson, M. C.*: *Lancet* 1: 674, 1935.
- (3) *Browne, J. S. L., and Venning, E. H.*: *Am. J. Physiol.* 116: 18, 1936.
- (4) *Browne, J. S. L., Henry, J. S., and Venning, E. H.*: *J. Clin. Investigation* 16: 678, 1937.
- (5) *Idem.*: *Ibid.* 17: 503, 1938.
- (6) *Smith, G. V. S., Smith, O. W., and Pincus, G.*: *Am. J. Physiol.* 121: 98, 1938.
- (7) *Wilson, R. B., and Randall, L. M.*: *Proc. Staff Meet. Mayo Clin.* 13: 813, 1938.
- (8) *Hain, A. M.*: *Edinburgh M. J.* 45: 678, 1938.
- (9) *Idem.*: *Quart. J. Exper. Physiol.* 29: 159, 1939.
- (10) *Browne, J. S. L., Henry, J. S., and Venning, E. H.*: *Am. J. Obst. & Gynec.* 38: 927, 1939.
- (11) *Dingemans, E., Laqueur, E., and Muhlbock, O.*: *Monatschr. f. Geburtsh. u. Gynäk.* 109: 37, 1939.
- (12) *Smith, G. V. S., and Smith, O. W.*: *Am. J. Obst. & Gynec.* 39: 405, 1940.
- (13) *Hain, A. M.*: *J. Endocrinol.* 2: 104, 1940.
- (14) *Cope, C. L.*: *Brit. M. J.* 2: 545, 1940.
- (15)

specimens were carried out by the technique of Cuyler and Baptist<sup>10</sup> which employed repeated washings of the extracts with alkali solutions to remove estrone, a 17-ketosteroid. The colorimetric estimations were done by the method of Oesting.<sup>11</sup> His method of calculation was employed and the amounts of 17-ketosteroids have been expressed in terms of international units of androsterone. These units may be converted into milligrams of crystalline androsterone by division by 10.

We recognize the fact that the data obtained do not interpret the bio-activity or chemical identity of the substances estimated.

As our previous communications have repeatedly pointed out, the values obtained by the method employed here have been consistently lower than most of the others reported, and comparison should be made with the excretion, as reported by us, in healthy women with normal ovarian function. This "yardstick" is based on the study of 13 normal women. The criteria for normality included: excellent general health; satisfactory general physical examination; absence of signs and symptoms of endocrinopathy; age range of 21 to 43 years; cyclic and quantitatively normal menses; normal urinary excretion of the pregnanediol-complex; and in most instances the association of well proliferated progestational endometria with bleeding. Serious effort has been made to eliminate variables; one of us (E. C. H.) has interpreted all endometrial biopsy material, and one individual has made all of the colorimetric readings.

The average normal daily excretion ranged from the equivalent of 15 to 47 I.U. of androsterone.

All patients whose urinary titers were quantified had received routine medical, gynecologic, and endocrine surveys. All had metabolic rate determinations and roentgenograms of the sella turcica.

#### PRESENTATION OF DATA

A total of 216 women has been studied, with 5,700 twenty-four-hour urine specimens having been quantified for 17-ketosteroids. These figures represent all of the women patients studied. Those reported on here are only a fraction of this number.

*Virilizing Syndrome.*—To us at present, the chief interest of these observations on the excretory values of 17-ketosteroids in hirsutism and virilizing syndromes lies in the fact that they concern patients in whom, by fact or by theory, the primary endocrine disturbance is hyperactivity of the adrenal cortex, and the secondary endocrine disturbance is hypofunction of the ovaries. These data, representing, therefore, potential measurements of varying degrees of primary hyperactivity of the adrenal, are to be compared with similar data submitted in the other groups in which the endocrine disturbance of patients is primarily ovarian. Also this comparison is for the purpose of testing a theory previously expressed by members of our group<sup>3, 4, 8, 9</sup> that a balance exists between estrogenic ovarian and androgenic adrenal functions which is upset by ovarian failure in the direction of increased adrenal activity. The data can serve as a valuable "measuring stick" as to the quantitative expectations in urinary 17-ketosteroids values when the adrenal cortex becomes hyperactive.

# EVALUATION OF COLORIMETRIC QUANTITATION OF 17-KETOSTEROIDS\*

## APPLICATION IN GYNECOLOGY

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THE gynecic role of androgens has never been fully explained. During the past years various members of our group have accumulated data and made reports on the excretion of 17-ketosteroids under different conditions. In one of the first communications,<sup>1</sup> we stated our agreement with Korenchevsky<sup>2</sup> that it does not seem accidental that these substances are found in the female, and before the judicious employment of sex hormone preparations in gynecologic therapy is possible, an effort should be made to isolate and identify these hormones, the properties of these hormones alone and in combination with the female hormones be learned, their ratio established, and alterations during endocrine and gynecologic disturbances be ascertained. Subsequent reports,<sup>3-9</sup> especially by certain members of the group (E. C. H. and W. K. C.), have partially answered some of the questions and have advanced ideas as to the origin of the 17-ketosteroids.<sup>3, 4, 8, 9</sup>

This communication embraces the study of 216 women who had 5,700 twenty-four-hour specimens of urine quantified for 17-ketosteroids. According to various subjective and objective findings, the patients reported on were classified into 4 groups. The rationale of this grouping will be explained under each group. Significant information regarding the estrogen, progesterone, and androgen relationship seems desirable at this time, since there has been rather extensive use of androgens in the treatment of most functional conditions in women, for which previously estrogens have been reported to have been of value.

In selecting the patients for study, it would seem logical that varying degrees of ovarian failure would be most likely to reflect alterations in androgen and estrogen levels. Related information would be obtained by choosing patients showing virilizing symptoms.

## METHODS OF STUDY

Consecutive twenty-four-hour specimens of urine were collected for estimation of 17-ketosteroids during the whole interval between menstrual flowings when feasible, and the report was the average of these individual values. The urine was refrigerated during the time of collection and until it was examined. Hydrolyses and extractions of the

\*Read by Dr. Ross at the Sixty-sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

Data taken from thesis submitted by W. Kenneth Cuyler in partial fulfillment of requirements for the Ph.D. degree in Duke University, 1941.

do not differ greatly whether these symptoms be produced by injection or are spontaneous andromimetic responses. In our experience there has been a general tendency for the elevation of 17-ketosteroids to parallel the virilization or hirsutism; however, there were notable exceptions. As a rule, the patients with verified adrenal cortical hyperplasia yielded the highest titers. The three patients with diabetes associated with slight hirsutism had practically normal values. Others<sup>12</sup> have reported lowered levels in diabetes mellitus. The explanation probably lies in undernutrition and metabolic disturbances.

**Menometrorrhagia.**—Patients who experience too frequent or excessive uterine bleeding of functional origin may have diverse grades of ovarian failure. The grades of their ovarian disturbances can be gauged roughly by studies of endometrial biopsies taken at the onset of episodes of bleeding. Data from these studies as well as from a mass of clinical observations support the point of view that few of these

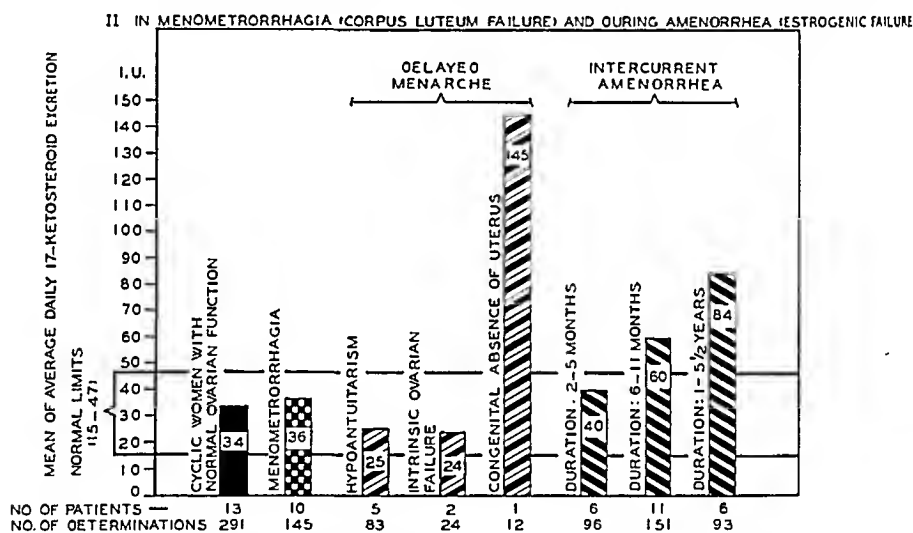


Fig. 2.—Urinary excretion of 17-ketosteroids in women with normal ovarian function and with ovarian failure. (The 17-ketosteroids were extracted by the method of Cuyler and Baptist and were estimated colorimetrically by the method of Oesting.)

patients exhibit any objective evidences of basic estrogenic deficiency, although intercurrent episodes of relative estrogenic deficiency obviously account for their menometrorrhagia.<sup>4</sup> As a rule, these individuals are well feminized, lack the endocrinopathic signs of glandular diseases, and are not possessed of hypoplastic sexual organs. Their ovarian disturbance concerns progesterone rather than the estrogens, being characterized by minimal or no corpus luteum activity. The proper selection of a group of patients with functional menometrorrhagia, characterized endocrinologically by deficiencies in corpus luteum function and not by any gross disturbances in estrogenic levels, permits study of the influence of simple corpus luteum failure of the ovaries upon the urinary excretion of 17-ketosteroids.

Ten women who presented the symptoms of excessive or too frequent uterine bleeding were studied. This was the only symptom of endocrine disease that was present. In none had therapeutic measures

In this group (Fig. 1) there were 34 women who presented definite virilizing syndromes with obvious, and often masculine, hirsutism associated with secondary ovarian failure. The ages varied from seventeen to forty-eight years. According to their physical findings and symptomatology, they fell into 4 clinical groups: 3 patients with hirsutism and diabetes mellitus; 15 with hirsutism not associated with obvious endocrine disease; 13 patients with presumed adreno-genitalism; and 3 patients with adrenal cortical hyperplasia proved at operation. A total of 381 titers was run on these patients, an average of 11.2 titers per patient.

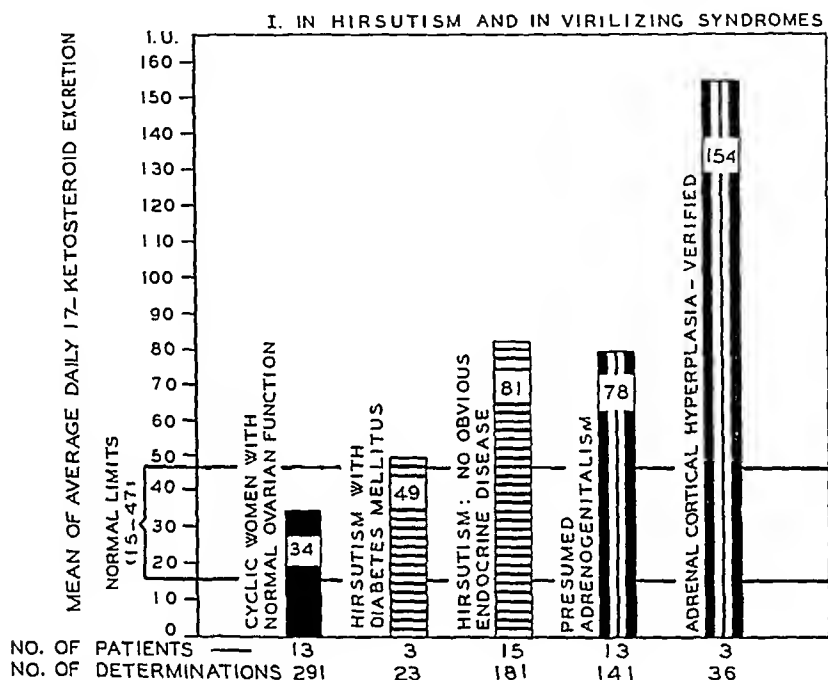


Fig. 1.—Urinary excretion of 17-ketosteroids in women with normal ovarian function and with ovarian failure. (The 17-ketosteroids were extracted by the method of Cuyler and Baptist and were estimated colorimetrically by the method of Oesting.)

Only 4 of these patients excreted quantities of 17-ketosteroids which fell within normal range. Fifty-nine per cent showed only moderate elevation of the titers. These ranged from the upper limits of normal to 100 per cent increases, or twice the normal limit. Of these 20 patients, 4 had titers which were increased only 20 per cent. Ten patients, or 20.5 per cent, excreted amounts more than twice that of the upper limits of normal, which ranged from 84 to 228 I.U., which was equivalent to 100 to 400 per cent increases. It is interesting to note that these data do not differ greatly from those obtained upon women being treated with intramuscular injections of testosterone propionate, doses varying from 10 to 25 mg. at intervals of two days. In such patients the excretion of 17-ketosteroids varied from 18 to 300 per cent over pre-treatment levels. It is accepted generally that this type of treatment, if persistently carried out, will produce symptoms of virilism and hirsutism in the female. All of which suggest that the excretion values

to excrete small amounts of pregnanediol-complex and in these few instances to have endometriums in estrogenic proliferation. Patients with intercurrent amenorrhea of greater than five months' duration consistently show increased urinary excretion of the 17-ketosteroids, while only one of the six patients whose amenorrhea had lasted from two to five months excreted more than normal amounts. The 17 patients, with only 3 exceptions, showed definite increase in their excretions. When considered together, there was an increase of 40 per cent in the patients with amenorrhea of one or more years' duration over those whose amenorrhea had lasted only from six to twelve months.

*Climacteric.*—Estrogenic ovarian failure, more severe in degree than that which occurs in many instances of intercurrent amenorrhea during the reproductive period, occurs physiologically during the sexual aging of woman or may be induced by radium or roentgenologic therapy. Complete ovarian deficiency occurs in bilaterally oophorectomized

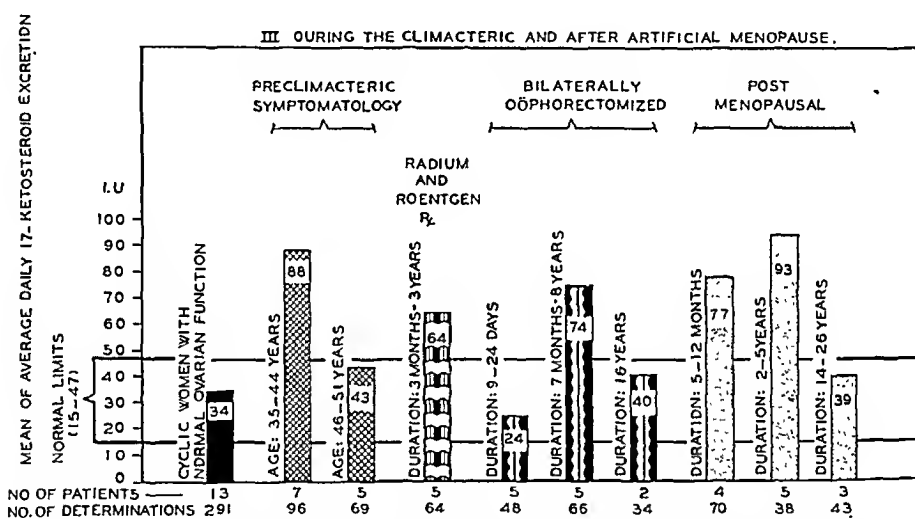


Fig. 3.—Urinary excretion of 17 ketosteroids in women with normal ovarian function and with ovarian failure. (The 17-ketosteroids were extracted by the method of Cuyler and Baptist and were estimated colorimetrically by the method of Oesting.)

women. In all of these instances, the causes of the failure may be reduced to a simple common denominator, intrinsic ovarian damage, resulting from senility, radium, roentgen ray, or surgery. Patients with this type of intrinsic ovarian failure afford an excellent opportunity for the investigation of possible alterations in the androgenic functions of the adrenals secondary to ovarian deficiency or deprivation. If the findings reported upon patients with amenorrhea were interpreted correctly, studies of 17-ketosteroids excretion during the climacteric and after artificial menopause should show similar, if not more marked, elevations to those during amenorrhea.

Forty-one women during the climacteric or after artificial menopause were studied. They were grouped according to the cause and degree of ovarian failure incidental to this state. A total of 528 determinations was made, an average of 12.9 per patient.

been instituted. A total of 145 urine specimens were quantitated, which was an average of 14.5 per patient.

The urinary titers of all these patients fell within normal limits, with the exception of two whose daily average was 49 I.U., which is only 2 above the upper normal of 47 I.U. This is in line with previous observations<sup>1, 4, 8, 13, 14</sup> that there is no significant alteration in the titers of patients who have functional menometrorrhagia, which we interpret as indicating that no progestin : androgen ratio exists. It would seem that varying degrees of corpus luteum function, ranging from normal to the absence of progestin secretion (as indicated by biopsy examination of the endometrium and pregnanediol-complex estimates) in itself has no effect on the level of 17-ketosteroid excretion and implies that such a phenomenon is not followed by secondary activity of the adrenal cortex as measured by the excretion of these steroids.

*Amenorrhea.*—Amenorrhea when due to disturbed ovarian function is associated commonly with signs of estrogenic deficiency, among which are hypoplasias or regressions in the sexual system, including atrophic alterations in the endometrium and vaginal mucosa. These objective manifestations of estrogenic deficiency are evidenced as failures of sexual maturation in adolescent hypo-ovarianism, and as sexual regressions in intercurrent hypo-ovarianism of the adult. As a rule, in adult hypo-ovarianism, the degree of sexual regression increases with the duration of the amenorrhea. Patients with adolescent and adult hypo-ovarianism, as characterized by primary or secondary amenorrhea, present the opportunity of investigating the influences of primary and secondary estrogenic deficiencies upon the urinary excretion of 17-ketosteroids, i.e., the androgenic activity of the adrenals.

Thirty-one patients with amenorrhea were studied. Those with adolescent ovarian failure had roentgenologic evaluation of their osseous ages. A total of 459 determinations was made, an average of 14.8 per patient. A number had studies of the pregnanediol-complex, and the majority had serial endometrial biopsies studied as an index to ovarian failure. In certain instances subsequent clinical responses to therapeutic measures, especially to gonadotropins and thyroid substance, aided in determining the cause of ovarian failure. Of this group, 8 patients, ages ranging from 15 to 26 years, had primary amenorrhea related to hypoantuitarism, intrinsic hypo-ovarianism or, in one instance, faulty somatic development of the uterus. All of these patients, except the last mentioned, showed little or no evidence of sexual maturity.

Six of the 8 patients with delayed adolescence excreted 17-ketosteroids in amounts that were below normal while 2 were within normal range. This may be explained by the deficient somatic and sexual development, as were reported in preadolescence,<sup>15</sup> or it might mean that hyperactivity of the adrenal cortex occurs only after intercurrent adult or late failure of the ovary.

Twenty-three patients, aged from 16 to 38 years, had intercurrent amenorrhea lasting from two months to five and one-half years. Those whose amenorrhea lasted under six months were found, on occasions,



urine extracts are estimated for total 17-ketosteroids, both active 17-ketosteroids and those with low androgenicity are measured, while the biologic method tests and measures the specific hormonologic effect of the androgens. The excretion tends to be lower in women than in men.

Although there is evidence in experimental animals that the ovaries may supply androgens, certain clinical evidences point to the adrenals as the chief source in the human being. These facts strengthen this thought: normal men and women excrete qualitatively identical androgens in almost similar amounts; the level of excretion is apparently higher in some eunuchoids than in certain males, while in true eunuchs the amounts excreted are low, but within normal limits; oophorectomized women immediately after operation may excrete smaller amounts than the average, but again overlap the normal range; the excretion in Addison's disease is low, while in patients with adrenal tumors the amounts are high. These facts may be ascertained by grouping the observations and recorded data of many workers.

In a general way it may be said that the average daily 17-ketosteroid excretion, expressed in international units of androsterone, corresponds numerically to the chronologic ages up until sexual maturity.

An analysis of the data suggests the theory of ovarioadrenal reciprocities, which are influenced chiefly by way of the pituitary. During early life and until adolescence is well advanced, the adrenopituitary interchange is dominant in steroid metabolism. When primary or adolescent hypo-ovarianism occurs and is of sufficiently severe grade to result in failure of sexual maturation, this axis retains its dominant position even during adult years. Under these circumstances, the level of adrenal function remains about that characteristic of late pre-adolescence. Normally, however, with the advent of adolescence and the beginning of full ovarian function, the ovaripituitary interchange is superimposed upon the primordial adrenopituitary one. The result is a harmonious arrangement wherein the pituitary becomes conditioned to working with both adrenals and ovaries and to being influenced, as regards its functions, by the regulatory effects of the intrinsic steroids of both the ovaries and the adrenals. During the reproductive period, the ovary and pituitary come to dominate the endocrine system. When, however, ovarian failure occurs from pathologic or physiologic causes, the pituitary, accustomed to being balanced in function by both the adrenal and ovarian steroids, is released in part from its inhibitions and, thereby, becomes hyperactive, then the adrenal cortex is stimulated to secrete greater quantities of steroids. The now dominant adrenopituitary interchange is stronger because of its previous conditioning by the ovary and pituitary. Eventually, however, stabilization occurs from the inhibiting effects of the increased amounts of adrenal steroids upon the function of the pituitary. The result is that during the late stages of sexual aging and during somatic senescence, the adrenopituitary axis becomes stabilized and steroid output reaches normal levels.

Most of our attention in the past has been directed to the pituitary-ovarian relationship. Lately the role of the endometrium has been

In Group I, there were 12 women between the ages of 35 and 51 years, none of whom had ceased to menstruate, who had symptoms that are generally recognized as due to spontaneous estrogenic deficiency associated with the menopause. The average daily titer of these patients was 36 to 121 I.U. with a mean average for the group of 69 I.U., which represents an increase of 50 per cent over the normal. It is interesting to note that the group from 35 to 44 years had a mean average of 88 I.U., while the mean average of the group from 46 to 51 years was 43 I.U. which places emphasis on age rather than the actual cessation of menses in the compensatory adrenal activity.

In Group II, there are 5 women who had had radium or x-ray therapy from three months to three years previously. The average daily titer was 49 I.U. which is consistent with our ideas of ovarian impairment following the use of such agents. It is difficult to judge with certainty when one can expect absolute hypo-ovarianism from these procedures.

In Group III, there were 12 women who had complete ovarian failure from previous bilateral oophorectomies. In order to get more exact information, they were further divided into 3 groups according to the time of operation.

Group A comprised 5 women whose operations had been done nine to twenty-four days before the time of the collection of the last twenty-four-hour specimen for study. Their daily average of excretion was 25 I.U.

Group B comprised 5 patients whose operations had been done seven months to eight years previously, and in these patients the daily titers were increased to an average of 74 I.U.

Group C comprised 2 patients whose operations had been done sixteen years previously, and both of these patients showed normal excretion value of 40.

In Group IV, there were 12 women who had had normal physiologic menapauses. They also are divided into three groups according to the length of time since the cessation of menstruation.

Group A comprised 4 women whose ages ranged from 42 to 49 years and whose elapsed time since menstruation was from five to twelve months. The excretion values in these women averaged 77 I.U., or 64 per cent increase.

Group B comprised 5 women whose ages ranged from 48 to 57 and whose elapsed time since menstruation was from two to five years. The excretion values averaged 93 I.U. or almost 100 per cent increase over upper limit of normal.

Group C comprised 3 women whose ages ranged from 62 to 74 years and whose elapsed time since menstruation was from fourteen to twenty-six years. The excretion values averaged 39 I.U., which was within normal range.

#### DISCUSSION

The androgenic substances obtained from the urine differ chemically from those obtained from endocrine glands, yet the three 17-ketosteroids: androsterone, dehydroisoandrosterone and the inactive eticholanol-3-17-one occur in the urine of normal men and women. When

17-ketosteroids were found in the patients of Group B. In Group C the urinary values of 17-ketosteroids were normal in women recently oophorectomized, i.e., nine to twenty-four days previously; these were increased definitely in women whose operations had been done from seven months to six years previously; and these titers were normal in 2 women, whose operations had occurred sixteen years previously. Quite similar findings were encountered in Group D: urinary titers of 17-ketosteroids were increased in those women whose menopause had occurred from five to twelve months and from two to five years previously, the latter group showing the higher values. In those women whose menopauses had occurred fourteen to twenty-six years previously the urinary titers of 17-ketosteroids were essentially normal.

The findings agree well with those of patients with amenorrhea due to intercurrent ovarian failure and are believed to support the thesis that adult estrogenic ovarian failure is followed by adrenal hyperactivity. Adrenal hyperactivity under these circumstances is considered to be an expression of the reciprocal arrangement between the adrenopituitary and ovaripituitary relationships which work through the pituitary. Theories based upon these reciprocities are applied to ovarian failure in general and to the hormonologies of the climacteric and somatic aging.

The application of this method of quantitation might be of value clinically in the following: as a test in rare malignant tumors of the adrenal and various virilizing syndromes; as a check in adrogenic therapy; as an aid in prognosing severe ovarian failure.

#### REFERENCES

- (1) Hamblen, E. C., Ross, R. A., Cuyler, W. K., Baptist, M., and Ashley, C.: *Endocrinology* 25: 491, 1939.
- (2) Korenchevsky, V.: *Brit. M. J.* 2: 896, 1937.
- (3) Hamblen, E. C., and Cuyler, W. K.: *J. A. M. A.* 113: 38, 1939.
- (4) Hamblen, E. C.: *Endocrine Gynecology*, Springfield, Ill., 1939, Charles C Thomas.
- (5) Hamblen, E. C., Cuyler, W. K., and Baptist, M.: *Endocrinology* 27: 16, 1940.
- (6) Hamblen, E. C., Pattee, C. J., and Cuyler, W. K.: *Ibid.* 27: 734, 1940.
- (7) Hamblen, E. C., Cuyler, W. K., and Axelsson, G. J.: *Ibid.* 28: 70, 1941.
- (8) Hamblen, E. C.: *J. Clin. Endocrinol.* 1: 180, 1941.
- (9) Hamblen, E. C., Cuyler, W. K., and Baptist, M.: *J. Clin. Endocrinol.* (In press.)
- (10) Cuyler, W. K., and Baptist, M.: *J. Lab. & Clin. Med.* 26: 881, 1941.
- (11) Oesting, R. B.: *Proc. Soc. Exper. Biol. & Med.* 36: 524, 1937; *Ibid.* 39: 76, 1938.
- (12) Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., and Reifstein, E. C., Jr.: *J. Clin. Endocrinol.* 1: 234, 1941.
- (13) Hamblen, E. C., Powell, N. B., Cuyler, W. K., and Pattee, C. J.: *Endocrinology* 26: 201, 1940.
- (14) Hamblen, E. C., Cuyler, W. K., Pattee, C. J., and Axelsson, G. J.: *J. Clin. Endocrinol.* 1: 211, 1941; *Ibid.* 1: 221, 1941.
- (15) Nathanson, I. T., Towne, L. E., and Aub, J. C.: *Endocrinology* 24: 335, 1939.

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#### DISCUSSION ON PAPERS OF DRS. ROSS AND ASSOCIATES AND BACHMAN

DR. THOMAS KENNETH BROWN, St. Louis, Mo.—Cohen and Marrion found that both estrone and estriol were excreted in combined form, for the most part as esters of glucuronic acid. They observed striking variations in the partition of combined and free estrone and estriol just prior to the onset of labor. They found that labor was preceded or accompanied by a decrease in the total amount of estrogens, but an increase in the free forms of them.

Browne and Venning found that pregnanediol is excreted in relatively small amounts during the first two to three months of pregnancy and that its urinary titer decreased rapidly just prior to the onset of labor.

Through the kindness of Dr. Willard M. Allen, I should like to show two slides which illustrate the daily determinations of sodium pregnanediol glucuronidate pre-

appreciated, and now it seems orderly and proper that the adrenal must be considered as a more integral part of sex endocrinology.

In carrying out this method of 17-ketosteroid quantitation in this study, we have tried to evaluate its application as a test in gynecology. It would seem applicable as a method for grading various virilizing processes. In rare malignant tumors of the adrenal it should prove helpful.

We feel that the use of androgenic substances in gynecology are definitely limited<sup>8</sup> and would use this method as a further check on the progress of such therapy.

Finally it would seem that this method would aid in the prognostication as to the severity of ovarian failure.

#### SUMMARY

The urinary excretion of 17-ketosteroids was investigated in 34 women, whose ages ranged from 17 to 48 years and whose symptomatology of adrenal hyperactivity ranged from simple hirsutism of moderate degree to states of marked virilization. The values varied from normal to 400 per cent increases. These data are regarded as comparable to those obtained after repeated injections at two-day intervals of moderate doses (10 to 25 mg.) of testosterone propionate.

In 10 women, whose ages ranged from 16 to 38 years and whose common symptom was menometrorrhagia related to simple corpus luteum failure of the ovaries, the values for urinary 17-ketosteroids did not differ from those of healthy cyclic women with normal ovarian function. It is inferred from these studies that progesterone plays no active part in the gonadopituitary reciprocities, as evidenced by this excretion study.

Eight patients, aged from 15 to 26 years, with delayed menarches, and 23 patients, aged 16 to 38 years, with amenorrhea, due to intercurrent ovarian failure, of durations which ranged from two months to five and one-half years, were studied. The majority of these patients exhibited physical signs of estrogenic deficiency. There was no elevation of the 17-ketosteroid titers in the group of patients with delayed menarche, while definite elevations in the titers occurred in the patients with amenorrhea due to intercurrent ovarian failure which had lasted six months or more. A correlation apparently existed between the duration of the amenorrhea and the amount of 17-ketosteroid excretion. These findings indicate that late or intercurrent estrogenic ovarian failure precipitates androgenic hyperfunction of the adrenal cortex.

There were 41 patients studied during the climacteric and after artificial menopause, and they were divided into four groups of women: Group A, 12 women, aged 35 to 51 years, with ovarian failure presumably due to premenopausal stage of the climacteric; Group B, 5 women, aged 39 to 45 years, with amenorrhea of relatively short durations, related to previous radium or roentgenologic therapy; Group C, 12 women, aged 21 to 48 years, with complete hypo-ovarianism due to bilateral oophorectomies; and Group D, 12 women, aged 42 to 74 years, who had experienced physiologic menopause.

The majority of the patients of Group A excreted increased amounts of 17-ketosteroids. No definite increases in the urinary values of

twice these values. As Dr. Ross has pointed out, investigations of this type must set up their own controls for the normal values.

As regards Dr. Ross' results a few comments may also be made:

a. The high values in the so-called virilizing syndrome are in accord with other reported observations.

b. The normal values in cases of menometrorrhagia are of considerable interest. The inference drawn from this finding that the corpus luteum plays no active part in the reciprocal relationships between gonads, anterior pituitary, and adrenal seems a step too far, however. The similarity of progesterone in its chemical structure to the other sex steroids and the apparent importance of the corpus luteum in controlling the duration of the sexual cycle makes it seem improbable to me that it has no effect on these glandular relationships.

Perhaps the most interesting of the observations are those showing a drop in 17-ketosteroid excretion immediately after castration, abnormally high values for some years thereafter, and finally a return to normal many years after the menopause. According to my understanding of Dr. Ross' paper, he suggests that in the presence of gonadal failure the adrenal becomes increasingly active and in a sense takes over the work of the ovary in balancing the anterior pituitary.

This seems to me a not unreasonable hypothetical explanation of the observed urinary findings. The absence of high 17-ketosteroids in primary ovarian failure seems perhaps to weaken the theory somewhat. There is no doubt, however, that the adrenal cortex plays an important part in the physiology of the sexual organs, and Dr. Ross' view on the exact nature of the adrenal's part in the sexual cycle is at least an interesting hypothesis to be worked on.

In general, certain reservations must be made in considering work based on the technique employed in these two presentations. Both the papers depend on the assumption that the excretion of the steroid hormones is somehow a measure of the functional activity of the glands from which they are derived. This is probably to some extent true, but limits must be placed on all inferences drawn from such data. Dr. Bachman has himself emphasized that the rates of urinary excretion of the steroid hormones do not depend only on the rate of their production, but are affected by utilization and destruction of the substances and by excretory mechanisms in the liver and kidney.

DR. SAMUEL H. GEIST, NEW YORK, N. Y.—Tests such as those employed by Dr. Ross in the measurement of urinary androgens have two purposes. One is simply to add to our physiologic knowledge. The second is to add to our armamentarium of therapeutic methods. Dr. Ross has indicated that definite amounts of hormonal substances are probably produced and excreted by every individual. One may infer that that substance has some physiologic value. It is probable also that the androgens have some therapeutic place in the treatment of the human female. I have been interested in that aspect of the androgen problem, but am perfectly willing to admit that our attempts have been mainly empirical. We have been advocating, however, the use of androgens in certain diseases.

The use of androgens in the female is still an experimental venture and simply because the literature reports good results in some cases, it does not by any means indicate that at the present time such substances should be used indiscriminately by the practitioner. If we will undertake our clinical investigations on that basis, we will make more modest claims and fewer mistakes. The future will decide the proper place of androgens in gynecologic disease.

DR. J. HOFBAUER, CINCINNATI, OHIO (by invitation).—In discussing the various factors which may be concerned in the onset of labor, postpituitary secretion should not be omitted. May I refer to my paper published in 1928, and also to a more recent report by Chang and Lin Noble. In their experiments, dogs' heads were perfused with Ringer's solution. Following the electrical stimulation of the vagus nerves, a considerable increase of pituitrin secretion ensued. This observation may have a definite bearing on the intensification of the Braxton Hicks' contractions during the last few weeks of pregnancy. In view of the fact that the uterus is supplied by both sympathetic and parasympathetic nerve fibers, it is reasonable to assume that the aforementioned uterine contractions may be responsible for augmented secretion of pituitrin which, in turn, registers its effect on the pregnant uterus.

ceding delivery in which a rather definite downward trend is indicated. The first is a case of toxemia and twins with bag induction, performed at a time when the titer was low; the second case a cardiac patient in whom induction was attempted three times before labor ensued and this occurred when a definite drop in titer was noted. These will be reported elsewhere shortly.

I should like to ask Dr. Bachman if it may not be necessary to obtain daily determinations in order to indicate when labor is imminent?

As yet we know but little about the role of androgens in the human organism. Why are they present in both male and female? Their presence may further indicate the delicate endocrine balance which is present in our patients and should warn us against upsetting this balance either by the injudicious administration of hormones or unnecessary operative procedures. It should be our aim to attempt to maintain conditions as nearly normal as possible.

It is suggested in Dr. Ross' paper that with the cessation of ovarian function the adrenals "take over" to a certain extent, but that this substitute also begins to fail after some years. As yet Dr. Ross has not found the "Fountain of Youth" and the hope which might be expressed in the rise of androgen titer is probably "wishful thinking."

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—Dr. Bachman's paper may be considered in two aspects: in the light of the new technical procedures he has developed, and in relation to the contribution it makes toward the theories of the causes of the onset of labor.

A colorimetric method for the determination of the estrogens has been one of the real needs in this type of investigative work for a long time. If, as Dr. Bachman has said, he has devised and used a method which has an error of only 10 per cent, it should be of tremendous value. This accuracy is probably greater than that usually obtained by methods of bio-assay unless very large numbers of animals are used. Besides the high degree of accuracy the method has the additional advantages of speed and economy.

A feature of interest in Dr. Bachman's curves is the consistency of the level of estriol excretion. Most previous studies and our own experience have led to the belief that there were wide daily fluctuations in the excretion rates of the estrogens during pregnancy. It seems possible at least that these fluctuations were only apparent and due simply to the chance inaccuracies of the older method of extraction and bio-assay. In the pregnanediol determinations also it is noteworthy that the quantities excreted from day to day are relatively constant. This again may be the result of a gradual improvement of a somewhat difficult technique.

As you know there is some physiologic evidence to suggest that progesterone causes relaxation of the uterus, whereas the estrogens are thought to increase its irritability. As a result of these observations, the onset of labor has been ascribed to a decreased progesterone and increased estrogen effect on the uterus. Dr. Bachman's figures, indicating no significant rise or fall in the excretion rate of either of these substances before the beginning of labor, are rather strong though not complete evidence against this view. Incidentally it casts some doubt on the clinical attempts to induce labor by the administration of estrogens. On the other hand, Dr. Brown, in discussion, has submitted a slide more acceptable to the traditional view that a fall in progesterone activity precedes the onset of labor. These contradictory findings are but another example of the difference in results which may be arrived at in two excellent laboratories employing these rather difficult technical procedures. More work must evidently be done to settle this particular point.

Dr. Ross has presented the results of 5,700 determinations of twenty-four-hour excretion of 17-ketosteroids and on the basis of these data has suggested certain additions to our basic knowledge of the relationships between gonads, adrenals, and the anterior pituitary gland.

As Dr. Ross has said, the so-called 17-ketosteroids are a mixture of chemically related substances probably produced principally in the adrenal. The actual figures for the twenty-four-hour excretion of 17-ketosteroids vary greatly, depending upon the method used. Dr. Ross, for example, reports a normal range of 15 to 47 international units of androsterone equivalent, using the Cuyler and Baptist hydrolysis and extraction technique and the Oesting colorimeter. Using the Callow technique and the Evelyn photoelectric colorimeter, we have normal figures of nearly

(Tables I to VII). The gonadotropic hormone was administered at different times in the menstrual cycle to ascertain any change in ovarian response before, during, or after the occurrence of spontaneous ovulation. At operation, the ovaries were carefully inspected, particularly for evidence of recent stigmas of ovulation. Both ovaries were removed whenever possible. In younger individuals, a unilateral oophorectomy was performed and a segment taken of the contralateral ovary. Appropriate sections of the endometrium were cut and fixed immediately for correlation with the ovarian findings. Several cross sections were made of each ovary and representative portions stained for microscopic examination. In the latter part of this investigation, sufficient sections were examined to include all the cystic follicle structures that could be visualized grossly. In analyzing our results, consideration was taken of the patient's age, the dosage of the gonadotropin, the time in the menstrual cycle during which injections were given, the time of operation, and the relationship of the endometrial to the ovarian findings.

#### CRITERIA IN THE EVALUATION OF ARTIFICIALLY INDUCED OVULATION

The divergence of opinion regarding the ovarian reaction to gonadotropin administration reported in the literature has impressed us with the necessity for a standardization of the histologic criteria of an induced ovulation and its differentiation from spontaneous ovulation. This differentiation is of paramount importance since the test animal (the human female), in these experiments, ovulates spontaneously. It is important, therefore, in each instance, to make certain that the evidence of ovulation which may be found after gonadotropin administration is not a normal, spontaneous phenomenon. Gross estimation of the number of corpora lutea within an ovary is unsatisfactory, since even microscopically it may be difficult to judge the age of a corpus luteum. The state of the endometrium may be helpful, since it responds to cyclical changes in hormonal ovarian function. Although it is conceded that the endometrium occasionally does not accurately reflect the level of ovarian hormonal function<sup>2-4</sup> and that the effects of a *very recent* ovulation may not be conspicuous in the endometrium, a mature, current corpus luteum may be expected to cause secretory endometrial changes. Aside from the histologic details of a recently ruptured Graafian follicle, some of the criteria we have attempted to follow in judging an artificially induced ovulation include the following:

In those women who menstruate at regular four-week intervals, it may be assumed that ovulation normally occurs during the midinterval, roughly between the tenth and sixteenth days. If, following gonadotropic therapy, the ovaries are removed during the ovulatory stage and present a single, recently ruptured follicle or very early corpus luteum, such a finding cannot be regarded as a result of medication, since this may have been, and probably was, a normal, physiologic occurrence. If operation is performed during the postovulatory phase, the result can be considered positive only if, in addition to a current corpus luteum, a freshly ruptured follicle is found. When the ovaries are removed during the preovulatory period, a ruptured follicle must have occurred

## THE EFFECT OF GONADOTROPINS UPON THE HUMAN OVARY\*

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EVER since anterior pituitary gland and pregnancy urine extracts have been shown to exhibit gonadotropic activity in animals, gynecologists have been interested in determining whether similar effects could be produced in human beings. A potent gonadotropic substance would, for obvious reasons, be a valuable addition to the endocrine therapeutic armamentarium. Our interest in this subject goes back to 1933 when one of us (S. H. G.) reported the effects of chorionic gonadotropin upon the human ovary.<sup>1</sup> During the ensuing eight years, we have investigated the effects of a variety of gonadotropic substances upon the human ovaries, and in this communication we wish to present to you, briefly, the results of these studies.

All the available gonadotropic substances, viz., the gonadotropic factors derived from chorionic tissue, from the serum of pregnant mares and from the anterior lobe of the pituitary, were used singly and in several combinations. The effects of the gonadotropes upon the ovaries were studied with two questions in mind, viz., (a) can ovulation be induced in the human female by means of gonadotropin therapy? and (b) what histopathologic changes are produced by the gonadotropes?

### METHODS AND MATERIALS

Ninety-one women, varying from 25 to 50 years of age, were selected for this study. Laparotomy was indicated in each instance, usually for uterine fibromyomas. The menses, in most cases, were quite regular, though several presented an irregular cycle or menometrorrhagia. Four women were gravid at the time of operation, and 3 were postmenopausal. The age grouping included 2 in the third decade of life, 37 in the fourth decade, 50 in the fifth decade, and 2 who were 50 years of age. Whenever possible, a variety of commercial preparations of a particular gonadotropin was used. The hypophyseal gonadotropin was employed in 34 cases; the chorionic, in 5 (previous report in 1933 by Geist included 50 cases); the equine, in 22; a combination of hypophyseal and chorionic, in 5; a combination of hypophyseal and equine, in 9; a combination of chorionic and equine, in 10; and a combination of chorionic and stilbestrol, in 6. Whenever feasible, a preliminary endometrial biopsy, vaginal biopsy, and endometrial smear were taken for comparison with the posttherapy effects. Injections were given over one to several days, in varying doses as described in detail below

\*Read, by Dr. Geist, at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.



TABLE I. EFFECTS OF CHORIONIC GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	CHORIONIC GONADO- TROPIN GIVEN INTRAMUSCULARLY	NO. OF RAT UNITS	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	43	25-26	A.P.L.	4,000	16-17	18	Secretory	+	0
2	34	28	A.P.L.	500	11-15	16	Secretory	+	0
3	49	Post-menop.	A.P.L.	1,500	--	--	Hypoplasia	0	0
4	46	28	A.P.L.	25,000	28-32	33	Secretory	+	0
5	40	28	A.P.L.	25,000	32-36	37	Secretory	+	0

related with the postovulatory phase of the menstrual cycle and with secretory effects in the uterine endometrium. In 3 instances, a double corpus luteum was found. This high incidence could not be interpreted as other than an unusual coincidence, since the corpora lutea were identical in all respects, mature in development and more advanced than any follicle that could have been caused to rupture artificially during the few days preceding operation. Unless the time of oophorectomy is postponed several days beyond the period of stimulation by the gonadotropic hormone, only a recently ruptured follicle or very early corpus luteum can be expected to be the result of an induced ovulation.

*Hypophyseal Gonadotropin.*—The hypophyseal gonadotropins were administered to 34 patients varying in age from 32 to 50 years. Gonadotropic factor (Ayerst, McKenna and Harrison) was injected intramuscularly in doses of 350 to 16,500 R.U., over periods of one to ten days, while antuitrin (Squibb) was given in amounts of 275 to 4,250 R.U., over a period of three to seven days. The time in the menstrual cycle during which injections were given was sufficiently varied to include every possible phase.

The ovarian effects are tabulated in Table II. In no instance, despite extremely large doses in some cases, was ovulation induced. In 2 cases (Cases 4 and 14), double or twin corpora lutea were found. These were identical in appearance and of the same degree of maturity. Their occurrence in the postovulatory period and their development in relation to the time of the injections, permitted only the diagnosis of normal, current, twin ovulations.

Definite and sometimes conspicuous histologic changes were noted in a majority of the ovaries studied. Differences in age, duration of therapy, and the phase of the cycle in which the gonadotropin was used could not be correlated with the degree of ovarian change. In a general way, however, where larger doses were employed, more profound histologic effects were obtained.

No positive statements can be made as to any absolute increase in the number of cystic follicles. In a few instances only, there seemed to be an apparent increase. In approximately 25 per cent of the cases, the ovaries contained cystic follicles which were larger than the average, with increased production of follicular fluid. In half the cases, there

sufficiently early to remove all doubt of a coincident, short menstrual cycle, before it can be deemed a positive result. Furthermore, in women with irregular menses or metrorrhagia, in whom the time of spontaneous ovulation is uncertain, definite conclusions cannot be drawn if only a single, recently ruptured follicle is found, without an accompanying current corpus luteum and secretory endometrium.

#### CRITERIA IN EVALUATING HISTOLOGIC OVARIAN CHANGES

A major difficulty in reporting histologic changes in the follicular system of the human ovary has been the lack of data on what constitutes the normal variations, both qualitatively and quantitatively. This is understandable because (a) individual variations are marked; (b) the follicular system is constantly undergoing physiologic changes; and (c) there is no uniformity of response throughout the ovary. Accordingly, 25 untreated patients were examined to establish a basis of comparison. Many sections of each ovary were made, to include all cystic follicle structures. The number of cystic follicles were found to be so varied that a mean average, though satisfactory statistically, would be of no great practical value. The presence, in the treated cases, therefore, of more than the average number of follicles, cannot be considered a definite indication of stimulation by the administered gonadotropin. However, an especially large number of follicle cysts was recorded as an increase. The control ovaries were particularly of aid in furnishing a basis of comparison for estimating the extent of granulosa cell activity, theca cell proliferation and theca interna luteinization.

#### RESULTS

*Chorionic Gonadotropin.*—Geist,<sup>1</sup> in 1933, studied the microscopic effects of antuitrin-S on the ovaries of 50 normally menstruating women. The dosage employed at that time was small (600 to 2,200 R.U.), and administered subcutaneously, over periods of thirty-six to one hundred hours. Though some changes were noted in the majority of cases, they could not be considered of unusual significance. The observations of Ross<sup>5</sup> and Hamblen<sup>6</sup> appear to be in substantial agreement with those of Geist. Zondek<sup>7</sup> noted cystic alterations of the follicles following the use of pregnancy urine gonadotropes, and with extremely large doses (26,500 R. U.), observed the presence of 4 corpora lutea in an enlarged ovary of a 30-year-old woman. Mandelstamm and Tsehaikowsky<sup>8</sup> found degenerative changes in maturing follicles, an increase in the number of follicle cysts and numerous corpora lutea. Westman<sup>9</sup> also found recent corpora lutea as well as cystic follicles and hemorrhagic areas in the ovaries of 3 patients who had received 3,600 to 5,000 R.U.

To complete our observations on the ovarian histopathology induced by the chorionic gonadotropins, large doses of A.P.L. (Ayerst, McKenna and Harrison, 500 to 25,000 R.U.) were administered intramuscularly, over periods of two to five days, in 5 women varying in age from 34 to 49 years (Table I). The ovarian response could be summarized as follows:

There was no evidence of artificially stimulated ovulation (Table I). An active corpus luteum, when present, could in all instances be cor-

was evidence of a stimulated growth of granulosa cells lining the cystic follicles, and of the theca interna cells about them, with partial luteinization of the latter.

The follicle cysts were not uniform in appearance, some showing greater stimulation than others. Cystic follicles that had apparently progressed to an advanced state of atresia seemingly did not respond to hypophyseal gonadotropin stimulation. Others presented a granulosa cell lining of variable thickness but uniform cellular activity, similar to that seen in maturing follicles, except for the significant fact that they did not contain any ova. Another finding which merits particular attention was the presence of cystic follicles in which one portion of the wall was composed of a thickened layer of well-developed granulosa cells with mitotic figures, while another portion of the same follicle consisted merely of a flattened layer of inactive cells. Some of the follicle cysts were slightly convoluted in outline, with evidence of granulosa cell proliferation, and theca cell growth with conspicuous luteinization. These at first strongly suggested the histologic picture of a recently ruptured follicle except, however, that they were unruptured. Close scrutiny of numerous cross sections of the ovary containing one or more of the stimulated cystic follicles did not reveal the presence of ova or the degenerative remnants of ova within their walls. This fact along with the absence of growing follicles beyond that seen normally seems to point to the conclusion that *while the hypophyseal gonadotropin in the human female may stimulate those granulosa cells and theca interna cells in follicles undergoing atresia, which are still capable of response, it apparently does not induce follicular maturation.* In addition to increased size and follicular fluid content of the cystic follicles, granulosa cell and theca interna cell stimulation, fully half the cases presented evidence of perifollicular congestion and hemorrhage, similar to that seen following chorionic gonadotropin.

*Equine Gonadotropin.*—Reports by Watson, Smith, and Kurczok,<sup>10</sup> Morieard and Saulnier,<sup>11</sup> Siegmund,<sup>12</sup> and Westman<sup>9</sup> have indicated that follicle stimulation could be obtained in the human ovary with equine gonadotropin, but that ovulation with resultant corpus luteum formation did not follow. Ross<sup>5</sup> and Hamblen<sup>6</sup> have likewise been unsuccessful in producing ovulation with the mare serum gonadotropin. Hartman,<sup>13, 14</sup> working with adult monkeys, found a reasonable certainty of stimulated ovulation in only 7 of 104 cases. In 1938, Davis and Koff<sup>15</sup> reported single and multiple induced ovulation in women with the mare serum gonadotropin administered intravenously. To date, this work has been confirmed only by Siegler and Fein, who reported artificial ovulation in 16 of 30 women.<sup>16</sup>

Gonadogen (Upjohn), gonadin (Cutter) and anteron (Sehering) were administered intravenously or intramuscularly in 22 women varying in age from 30 to 46 years. In no instance was conclusive evidence of artificially induced ovulation found (Table III).

Of the 22 patients receiving equine gonadotropins, fully half presented ovaries that showed evidence of slight to moderate perifollicular hemorrhage and congestion (Fig. 1). Only a few gave indications of conspicuous cystic follicle enlargement, stimulation of the granulosa cells, or increased theca interna cell activity. The histologic ovarian changes may, therefore, be considered as differing only quantitatively from those induced by the other gonadotropins.

TABLE II. EFFECTS OF HYPOPHYSEAL GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	HYPOTHYSEAL GONADOTROPINS GIVEN INTRAMUSCULARLY	NO. OF RAT UNITS	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT FOLLICLE (C.R.F.)	INDUCED OVULATION
1	38	38	Gonad. Factor	16,500	22-4	6	-----	0	0
2	47	30	Gonad. Factor	4,500	14-17	18	Secretory	+	0
3	41	28	Gonad. Factor	3,000	18-19	28	Secretory	+	0
4	43	28	Gonad. Factor	1,500	15	19	Secretory	+	0
5	44	Menomet.	Gonad. Factor	9,000	33-35	36	Late Prolif.	+	0
6	46	28-35	Gonad. Factor	6,000	27-28	31	-----	0	0
7	32	28	Gonad. Factor	3,000	8-9	12	Secretory	+	0
8	36	28	Gonad. Factor	12,000	27-6	8	Proliferative	0	0
9	39	28	Gonad. Factor	6,000	Gravid 60	65	Decidua	+	0
10	37	31	Gonad. Factor	4,500	9-11	15	-----	0	0
11	44	28	Gonad. Factor	9,000	Gravid 60	124	Decidua	+	0
12	50	Postmenop.	Gonad. Factor	6,000	--	--	Hypoplasia	0	0
13	40	Irreg.	Gonad. Factor	4,500	18-20	22	Secretory	+	0
14	35	26	Gonad. Factor	9,600	17-21	23	Secretory	+	0
15	43	28	Gonad. Factor	6,600	26-28	29	Proliferative	0	0
16	43	28	Gonad. Factor	350	5-6	8	-----	0	0
17	45	23-25	Gonad. Factor	1,500	7-9	10	Proliferative	C.R.F.	0
18	37	28	Gonad. Factor	750	20-23	24	Secretory	+	0
19	42	28	Gonad. Factor	2,250	26-7	8	Proliferative	0	0
20	37	28	Gonad. Factor	1,600	26-4	5	Proliferative	0	0
21	40	28	Gonad. Factor	1,700	21-27	28	Secretory	+	0
22	38	Menomet.	Gonad. Factor	2,200	20-3	7	-----	0	0
23	40	28-30	Antuitrin	275	8-11	12	Proliferative	0	0
24	43	25	Antuitrin	750	19-23	24	Proliferative	0	0
25	38	28	Antuitrin	2,250	10-17	18	Proliferative	0	0
26	36	21	Antuitrin	1,000	--	--	Proliferative	0	0
27	39	28	Antuitrin	1,750	8-12	13	Proliferative	0	0
28	48	Menomet.	Antuitrin	4,250	--	--	Proliferative	0	0
29	40	28	Antuitrin	1,250	11-14	16	Late Prolif.	Early C.L.	0
30	46	21	Antuitrin	1,250	27, 1-4	5	Proliferative	0	0
31	48	27	Antuitrin	2,000	26-30	31	Proliferative	0	0
32	37	21-28	Antuitrin	500	5-7	8	Menstrual	+	0
33	45	28	Antuitrin	2,500	--	--	Decidua	+	0
34	42	Gravid	Antuitrin						

TABLE IV. EFFECTS OF A COMBINATION OF HYPOPHYSEAL AND CHORIONIC GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	HYPOPHYSEAL AND CHORIONIC GONADO- TROPINS GIVEN INTRAMUSCULARLY	NO. OF RAT UNITS	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	48	28	Gonad. Factor* A.P.L.	7,500 12,500	14-18 19-21	22	Proliferative	0	0
2	42	28	Gonad. Factor* A.P.L.	6,000 17,500	17-20 21-25	26	Secretory	+	+
3	43	26-27	Gonad. Factor* A.P.L.	4,500 5,000	2-4 5-6	7	Hyperplasia	0	0
4	25	28	Gonad. Factor* A.P.L.	10,500 17,500	23-28	29	Secretory	+	0
5	29	30	Gonad. Factor* A.P.L.	7,500 12,500	29-33	34	Secretory	+	0

\*Collip.

TABLE III. EFFECTS OF GONADOTROPINS DERIVED FROM THE SERUM OF PREGNANT MARES UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	EQUINE SERUM GONADOTROPIN	NO. OF UNITS	ROUTE*	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	37	28	Gonadogen†	60	IV	16	17	Secretory	+	0
2	39	28	Gonadogen	60	IV	21	22	Adv. Prolif.	0	0
3	46	28-35	Gonadogen	60	IV	23	24	Hyperplasia	0	0
4	35	28-30	Gonadogen	60	IV	13	14	-----	C.R.F.	0
5	39	28	Gonadogen	60	IV	22	23	Secretory	+	0
6	42	Menomet.	Gonadogen	60	IV	9	1	Proliferative	0	0
7	45	Menomet.	Gonadogen	60	IV	28	30	Adv. Prolif.	0	0
8	39	28	Gonadogen	90	IV	18	19	Secretory	+	0
9	45	30	Gonadogen	120	IV	20	21	Adv. Prolif.	C.R.F.	0
10	44	28	Gonadogen	120	IV	9-10	11	Early Secr.	+	0
11	42	28	Gonadogen	150	IV	12	13	Adv. Prolif.	+	0
12	32	23	Gonadogen	180	IV	12-15	16	Secretory	+	0
13	32	26-28	Anteron†	350	IM	9-15	16	Secretory	+	0
14	40	25-30	Anteron	500	IM	22-27	27	Late Prolif.	0	0
15	41	28	Anteron	500	IM	13-16	17	Secretory	+	0
16	39	26-28	Anteron	700	IM	1-6	11	Late Prolif.	C.R.F.	0
17	39	Menomet.	Gonadin§	1,200	IM	28-29	32	Secretory	+	0
18	37	Irreg.	Gonadin	2,400	IM	1-5	6	Proliferative	0	0
19	41	28	Gonadin	3,600	IM	10-15	16	Secretory	+	0
20	38	Irreg.	Gonadin	600	IM	28	34	Late Prolif.	0	0
21	30	28	Gonadogen	60	IV	29-31	26	-----	+	0
22	37	Irreg.	Gonadin	30	IV	22-24	34	Late Prolif.	C.R.F.	0
			Gonadin	1,000	IM	25				
			Gonadin	3,000	IM	26-30				
			Gonadogen	60	IV	30-32				

\*IV, Intravenously; IM, intramuscularly.

†Cartland-Nelson units.

‡International units.

§Cole-Saunders units.

*Combination of Hypophyseal ("Synergist") and Chorionic Gonadotropins.*—Five women, 25 to 48 years of age, received both hypophyseal and chorionic gonadotropins together or in succession, in either the pre- or postovulatory phases of the menstrual cycle. One case (Table IV,



Fig. 3A.—Case 2 (Table IV, Path. No. 66457), aged 42, had a normal menstrual cycle. Six thousand R.U. of gonadotropic factor and 17,500 R.U. of A.P.L. were given during the seventeenth to the twenty-fifth day of the cycle. Operation was performed on the twenty-sixth day. Section shows normal, active corpus luteum of current cycle.



Fig. 3B.—Endometrium showing secretory phase, corresponding to twenty-sixth day of the menstrual cycle.

Case 2) of possible artificially induced ovulation is described (Figs. 3A, 3B and 3C):

CASE 2.—Table IV. H. H., 42 years of age. Menses began at age of 13, occurred every twenty-eight days and lasted three days. She was admitted because of symptoms caused by multiple uterine fibromyomas. A total of 6,000 R.U. of gonadotropic factor was administered intramuscularly during the seventeenth to

## COMBINATION GONADOTROPIN THERAPY

The experimental studies of Leonard,<sup>17</sup> Evans and his co-workers,<sup>18, 19</sup> Engle and Hamburger,<sup>21</sup> and Mazer and Katz<sup>20</sup> have shown that hypophyseal gonadotropin administered with the chorionic hormone has a



Fig. 1.—Case 12 (Table III, Path. No. 66213), aged 32, had normal menstrual cycle. One hundred and eighty units of gonadogen were given intravenously on the twelfth to fifteenth day of the cycle. Operation was performed on the sixteenth day of the cycle. Section shows the most frequent effect noted after equine serum therapy, viz., perifollicular congestion and hemorrhage.



Fig. 2.—Case 10 (Table II, Path. No. 65301), aged 37, had menstrual interval of 31 days. Forty-five hundred R. U. of hypophyseal gonadotropic factor (Collip) were given intramuscularly on the ninth to eleventh day of cycle. Ovaries were removed on the fifteenth day. The follicle wall shows a serpinginous outline, without rupture. Such a picture may be easily confused with that seen soon after the rupture of a normal Graafian follicle.

synergistic effect. Recently, Mazer and Ravetz<sup>23</sup> have reported “stimulation and overstimulation of the ovaries in 20 of 23 patients” treated with a combination of hypophyseal and chorionic gonadotropins.



The histologic changes following the combination of hypophyseal and chorionic gonadotropins are similar to those seen after the hypophyseal gonadotropin alone, except that all of the 5 cases showed some measure of response. In 2 of the 5 cases, the intensity of reaction was marked. This, however, could not be attributed to a synergistic action, since equally pronounced effects were encountered in which an equivalent or smaller amount of hypophyseal gonadotropin was used. Mazer and Ravetz<sup>23</sup> recently reported profound changes in the human ovary with the use of synapoidin (Parke, Davis & Co.), a combination of chorionic gonadotropin and a pituitary extract containing very little of the gonadotropic substance. In 16 patients the authors found "multiple hemorrhagic follicles with luteinized granulosa layers in all but one, multiple small and large aberrant corpora lutea, hemorrhage into the stroma and intense edema." In our cases, such synergistic activation was not evident.

*Hypophyseal and Equine Combination.*—A combination of hypophyseal and equine gonadotropins was used in 9 patients, 36 to 46 years of age. These were given concurrently or one before the other, over periods of several days. The dosage of anteron varied from 800 to 16,000 units, and the gonadotropic factor from 6,000 to 15,000 R.U. In one of the 9 cases, the gross and histologic evidence suggested the possibility of a single induced ovulation (Case 1, Table V). The microscopic features in this instance were similar to those produced by the hypophyseal and chorionic gonadotropin. The combined use of hypophyseal and equine gonadotropins resulted in histologic changes which did not differ noticeably from those following the administration of the hypophyseal factor alone. Augmentation of the stimulating effects was not observed.

*Combination of Equine and Chorionic Gonadotropins.*—In 10 cases, a combination of equine and chorionic gonadotropes was employed. The total dosage of A.P.L. varied from 5,000 to 25,000 R.U.; of gonadogen, from 90 to 350 units; of anteron, from 10,800 to 12,000 units; and of gonadin, from 1,000 to 5,400 units. Artificial ovulation did not result (Table II). The histologic changes were definitely less marked than following any of the combinations which included the hypophyseal factor.

*Combination of Chorionic Gonadotropin and Stilbestrol.*—(Table VII) Williams<sup>24</sup> has reported an augmentation of the gonadotropic effect of pregnant mares' serum in animals simultaneously receiving stilbestrol. Pencharz<sup>25</sup> showed a similar synergistic action in animals with chorionic gonadotropin and certain estrogens. Simpson, Evans, Fraenkel-Courat and Hao Li<sup>26</sup> combined stilbestrol with chorionic gonadotropin in hypophysectomized rats.

To ascertain if this effect was applicable to the human female, 6 cases, varying from 37 to 50 years of age, were given chorionic gonadotropin and stilbestrol (Table VII). Histologic examination of the ovaries failed to reveal evidence of induced ovulation or of any synergistic action. The perifollicular hemorrhage or congestion was no greater than has been encountered in cases treated with chorionic gonadotropin alone.

the twentieth day of the cycle, in daily doses of 1,500 R.U.; 17,500 R.U. of A.P.L. were given from the twenty-first to the twenty-fifth day of the cycle, by daily, intramuscular injections of 2,500 R.U. At operation, performed on the twenty-sixth day, the right ovary contained a mature corpus luteum, while the left ovary revealed the presence of a recent stigma, the minute opening containing an adherent blood clot. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed.

*Gross Pathology of the Ovaries.*—The right ovary was normal in size and configuration. A corpus luteum was present which on section appeared to be that of the current menstrual cycle. Several sections through the ovary revealed a few small, 3 to 4 mm., cystic follicles, 2 of which showed slight hemorrhage in their walls. The left ovary was normal in size. Section revealed a cystic follicle measuring 1.25 cm. in diameter, in addition to 4 small follicle cysts, the walls of which had a suggestive bluish tinge. A small punctum containing blood was seen, which when cut was found to be connected with a collapsed follicle with grayish, hemorrhagic walls.

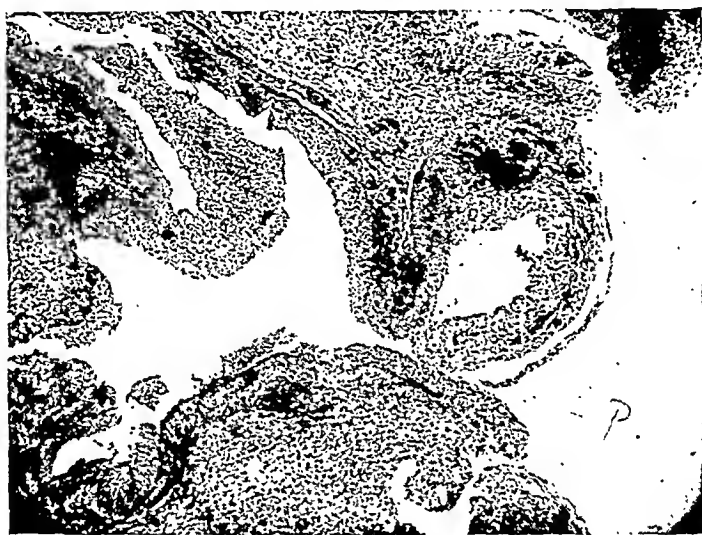


Fig. 3C.—Ruptured follicle, resembling recent ovulation. Note serpiginous wall; granulosa cell growth; theca proliferation and luteinization; perifollicular hemorrhage and punctum.

*Microscopic Examination.*—The corpus luteum structure found in the right ovary presented the characteristics of a normal, mature, active structure which would correspond to that expected on the twenty-sixth day of the cycle (Fig. 3A). The uterine endometrium, likewise, showed an advanced secretory phase (Fig. 3B). The collapsed, ruptured follicle in the left ovary showed the histologic characteristics found in a recently ruptured Graafian follicle, viz., irregular, serpiginous outline, an inner layer of active follicle cells not yet luteinized, and proliferating theca interna cells with conspicuous luteinization (Fig. 3C). In addition, there was marked hemorrhage and congestion about the theca interna and particularly at the point of rupture. The other cystic follicles were atretic follicles with a varying degree of granulosa cell and theca cell stimulation and perifollicular hemorrhage and congestion.

Although the evidence suggests an artificially induced, additional ovulation late in the postovulatory phase, this diagnosis is open to question. The same picture may be produced by rupture of a stimulated, cystic follicle near the ovarian surface by increase in follicle fluid and disruption of the thin segment of ovarian tissue by excessive perifollicular hemorrhage.

TABLE VI. EFFECTS OF A COMBINATION OF EQUINE SERUM AND CHORIONIC GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	EQUINE SERUM AND CHORIONIC GONADOTROPINS	NO. OF UNITS	ROUTE	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	48	28	Gonadogen* A.P.L.	200 U. 5,000 R.U.	IV IM	35-38 39-41	50	Proliferative	0	0
2	49	28	Gonadogen* A.P.L.	180 U. 10,000 R.U.	IV IM	26-29 30-32	33	Secretory	+ (double)	0
3	47	28	Gonadogen* A.P.L.	170 U. 10,000 R.U.	IV IM	24-27 28-30	33	Proliferative	0	0
4	36	28	Gonadogen* A.P.L.	350 U. 7,500 R.U.	IV IM	24-30 28-30	31	Late Prolif.	+	0
5	47	28	Gonadogen* A.P.L.	120 U. 7,500 R.U.	IV IM	30 32-34	35	Proliferative	0	0
6	47	Postmenop.	Gonadogen* A.P.L.	90 U. 15,000 R.U.	IV IM	Postmenopausal		Hypoplasia	0	0
7	34	28	Anteron A.P.L.	10,800 I.U. 22,500 R.U.	IV IM	16-23	24	Secretory	+	0
8	31	28	Anteron A.P.L.	12,000 I.U. 25,000 R.U.	IV IM	27 and 1-9	10	Early Secretory	C.R.F.-(double)	0
9	30	28	Gonadin A.P.L.	5,400 U. 12,500 R.U.		37-41 42-44, 1-2	3	Proliferative	0	0
10	30	28	Gonadogen* Gonadin† A.P.L.	100 1,000 17,500 R.U.	IV IM IM	5-7 6 8-11	12	Secretory	+	0

\*Cartland-Nelson unit.

†Cole-Saunders unit.

TABLE V. EFFECTS OF A COMBINATION OF HYPOPHYSEAL AND EQUINE SERUM GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	HYPOPHYSEAL AND EQUINE SERUM GONADOTROPINS	NO. OF UNITS	ROUTE†	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	40	28	Gonad. Factor* Gonadin	6,000 R.U. 3,000	IM IM	19-22 19-23	24	Secretory	+	+
2	45	28	Gonad. Factor* Gonadin	10,500 R.U. 3,000	IM IM	Gravid		Decidua	+	0
3	44	Menomet.	Gonad. Factor* Anteron	6,000 R.U. 1,200 I. U.	IM IV	--	+1	Proliferative	0	0
4	38	25-30	Gonad. Factor* Anteron	6,000 R.U. 1,200 I.U.	IM IV	30, 1-3 3-5	6	Proliferative	0	0
5	46	26-40	Gonad. Factor* Anteron	15,000 R.U. 14,000	IM IV	17-24 18-24	25	Proliferative	0	0
6	44	29	Gonad. Factor* Anteron	12,000 R.U. 16,000	IM IV	13-20	21	Proliferative	0	0
7	44	28-30	Gonad. Factor* Anteron	12,000 R.U. 10,000	IM IV	28, 1-7 3-7	8	Proliferative	0	0
8	36	28	Gonad. Factor* Anteron	6,000 R.U. 800	IM IV	13-15 11-12	16	Secretory	+	0
9	38	30	Gonad. Factor* Anteron	12,500 R.U. 10,000	IM IV	19-23	24	Proliferative	0	0

\*Collip.

†IM, Intramuscular; IV, intravenously.

## SUMMARY

The effect of a variety of gonadotropins upon the human ovary was studied in a series of 91 cases.

The following gonadotropins were used: hypophyseal, chorionic, pregnant mares' serum; combination of chorionic and hypophyseal, chorionic and equine, and chorionic and stilbestrol.

The histologic alterations in the human ovary caused by the various gonadotropins differed quantitatively rather than qualitatively. The intensity of reaction was most marked following the hypophyseal gonadotropins, decidedly less with equine, and least with the chorionic gonadotropins. The histopathologic ovarian changes in the majority of instances in which the hypophyseal gonadotropin was administered, included enlargement of cystic follicles, proliferation of the granulosa cells lining these follicles, proliferation and luteinization of the theca interna cells, perifollicular congestion and hemorrhage, and occasional edema and congestion of the ovarian parenchyma. With the equine gonadotropin, similar alterations were noted, but in a smaller percentage of cases and to a lesser degree. The only conspicuous effect of the chorionic gonadotropin was the production of perifollicular congestion and hemorrhage.

No synergistic effects were observed with any of the gonadotropin combinations. The response to the hypophyseal and chorionic or the hypophyseal and equine gonadotropins did not materially differ from those following the use of the pituitary extract alone. The combination of equine and chorionic gonadotropins had no greater effect than that induced by the sum of the individual components. Stilbestrol was not found to enhance the activity of the chorionic hormone.

In no instance was evidence of ovulation found which could be unquestionably attributed to the administered gonadotropins.

The absence of any increase in the number of maturing Graafian follicles, the absence of ova or degenerative remnants of ova in the cystic follicles, and the absence of induced ovulations suggests that, while the available gonadotropins may stimulate those granulosa and theca interna cells, in follicles undergoing atresia, which are still capable of response, they apparently do not induce follicle maturation or stimulate the development of follicles containing normal ova to maturity and ovulation.

For the materials used in this investigation, we are indebted to the following: Schering Corporation, anteron, pranturon; Ayerst, McKenna and Harrison, Ltd., A. P. L., gonadotropic factor, stilbestrol; Cutter Laboratories, gonadin; The Upjohn Company, gonadogen; Eli Lilly and Company, stilbestrol; E. R. Squibb & Sons, antuitrin.

## REFERENCES

- (1) Geist, S. H.: *AM. J. OBST. & GYNEC.* 26: 588, 1933.
- (2) Hamblen, E. C., Ashley, C., and Baptist, M.: *Endocrinology* 24: 1, 1939.
- (3) Hamblen, E. C.: *Endocrinology* 24: 13, 1939.
- (4) Ross, R. A.: *South. M. J.* 32: 52, 1939.
- (5) Ross, R. A.: *AM. J. OBST. & GYNEC.* 34: 780, 1937.
- (6) Hamblen, E. C.: *Endocrinology* 24: 848, 1939.
- (7) Zondek, B.: *Arch. f. Gynäk.* 144: 133, 1930.
- (8) Mandelstamm, A., and Tschalikowsky, W. K.: *Arch. f. Gynäk.* 151: 686, 1932.
- (9) Westman, A.: *Zentralbl. f. Gynäk.* 59: 1090, 1935.
- (10) Watson, B. P., Smith, P. E., and Kurzrok, R.: *AM. J. OBST. & GYNEC.* 36: 562, 1938.
- (11) Moricard, F., and Saulnier, F.: *Bull. Soc. Gynec. et d'obst.* 27: 132, 1938.
- (12) Siegmund, H.: *Zentralbl. f.*

TABLE VII. EFFECTS OF A COMBINATION OF CHORIONIC GONADOTROPINS AND ESTROGENS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	CHORIONIC GONADOTROPIN AND STILBESTROL	DOSAGE	ROUTE*	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	45	28	A.P.L. Stilbestrol	25,000 R.U. 25 mg.	IM PO	31-35	36	Secretory	+	0
2	37	27	A.P.L. Stilbestrol	25,000 R.U. 25 mg.	IM PO	13-17	18	Secretory	+	0
3	45	21	Stilbestrol Pranturon	15 mg. 4,500 I.U.	PO IM	10-13 12-13	14	Early Secr.	+	0
4	50	28	Stilbestrol Pranturon	22 mg. 3,750 I.U.	PO IM	20-23 21-23	24	Secretory	+	0
5	38	28-30	Stilbestrol Pranturon	36 mg. 11,250 I.U.	PO IM	22-29 25-29	30	Adv. Prolif.	0	0
6	40	30	Stilbestrol Pranturon	31 mg. 9,000 I.U.	PO IM	18-24 21-24	25	Secretory	+	0

\*IM, Intramuscularly; per os.

that although the findings are negative and we can accept them only with reserve, the work is a tremendous step forward, and this study should form the basis for further studies which will be more fruitful, particularly if younger subjects and perhaps other synergistic substances can be employed with the gonadotropic substances.

DR. EMIL NOVAK, BALTIMORE, MD.—There is much need of just such papers as this. The problem is not an easy one to approach experimentally in the human female, because of the difficulty of proper scientific control. Anyone familiar with the structure of the ovary knows the enormous variation in the histology of individual ovaries, even within the limits of normality. While Dr. Geist made genuine efforts to control his studies, there are few of the pictures which he has shown in ovaries which had been treated by gonadotropes which are not encountered in the routine laboratory study of ostensibly normal ovaries.

The objections which are urged by Dr. Traut are valid, although I do not believe they are of decisive importance in evaluating the results of this study. What we are hoping for with gonadotropic preparations is an effect as striking as that seen, for example, in the ovaries of certain experimental animals, an effect so clear-cut as to leave nothing to the imagination, such as pronounced follicle-ripening, luteinization, and ovulation. Such effects Dr. Geist, in common with a number of excellent investigators, and in contrast with one or two authors whose results have been much publicized by manufacturers, has been unable to obtain.

Mention has been made of the remarkable ovarian reaction seen in some cases of hydatidiform mole and chorionepithelioma. The pertinence of this to the present problem has seemed to me to have been insufficiently stressed. When we can explain this reaction satisfactorily we will have advanced a long way in our knowledge of the mechanism of gonadotropic activity in the human ovary.

The extreme ovarian response in hydatidiform mole and chorionepithelioma is at least the indirect result of an exaggerated chorionic gonadotrope production, and yet such studies as Dr. Geist has reported indicate that this same hormone has little effect upon ovarian histology. How can this seeming paradox be explained? The natural suggestion would seem to be that the ovarian reaction in these abnormal pregnancy conditions is due to the pituitary rather than the chorionic gonadotropic principles, and that the latter serve in some way to motivate or activate the former. The problem is still unsolved, in spite of much experimental study, such as that of Evans and his associates.

Finally, such papers as this should serve a valuable purpose in curbing the present therapeutic abuse of so-called gonadotropic commercial preparations. I know of none which have been more widely misused in the past two years than the hormone preparations of pregnant mare's serum. All over the country today sterile women are receiving "shots" of this substance, usually on the basis of very inadequate study, often in the absence of any endocrine dysfunction whatsoever, and almost always with no benefit. There can be no objection to a discriminating employment of the equine gonadotrope, experimental though it still is, but we should take a firm stand against the slipshod use of this and other gonadotropes which are now so widely prevalent.

DR. J. HOFBAUER, CINCINNATI, OHIO (by invitation).—I believe that the utilization of gonadotropins at present available, should be discarded. They have not proved of value in stimulating ovarian function. Our observation of the formation of multiple cysts in the ovary following its use may serve as a warning.

A specific gonadotropin factor is available, however, by the application of low dosage x-ray to the pituitary as recommended by me in 1922 and 1923. Observations of recurrence of menstruation and ovulation, and occasionally pregnancy, combine to recommend this method, if used with caution and discernment.

DR. GEIST (closing).—I am in accord with Dr. Traut on most of the points. As far as the age of the patient is concerned, the patients of 25 showed no variation from those of more advanced age. I do not believe one can accuse a woman of 35 of possessing "refractory ovaries."

Gynäk. 62: 2113, 1938. (13) *Hartman, Carl G.*: Cooperation in Research, Carnegie Inst. of Wash., Pub. No. 501, 389, 1938. (14) *Idem*: Bull. Johns Hopkins Hosp. 63: 351, 1938. (15) *Davis, M. E., and Koff, A. K.*: AM. J. OBST. & GYNEC. 36: 183, 1938. (16) *Siegler, S. L., and Fein, M. J.*: Ibid. 38: 1021, 1939. (17) *Leonard, S. L.*: Proc. Soc. Exper. Biol. & Med. 29: 812, 1932. (18) *Evans, H. M., Meyer, K., and Simpson, M. E.*: Ibid. 21: 845, 1931. (19) *Idem*: Am. J. Physiol. 100: 141, 1932. (20) *Mazer, C., and Katz, B. R.*: Endocrinology 17: 709, 1933. (21) *Engle, E. T., and Hamburger, C.*: Proc. Soc. Exper. Biol. & Med. 32: 1531, 1935. (22) *Buttner, W.*: Arch. f. Gynäk. 163: 487, 1937. (23) *Mazer, C., and Ravetz, E.*: AM. J. OBST. & GYNEC. 41: 474, 1941. (24) *Williams, P. C.*: Nature 145: 388, 1940. (25) *Pencharz, R. I.*: Science 91: 554, 1940. (26) *Simpson, M. E., Evans, H. M., Fraenkel-Courat, H. L., and Hao Li, Choh.*: Endocrinology 28: 37, 1941.

4 EAST EIGHTY-EIGHTH STREET

## DISCUSSION

DR. HERBERT F. TRAUT, NEW YORK, N. Y.—If I am correct, the authors conclude that none of the gonadotropic substances used, singly or in combination with other substances, produced conclusive evidence of the maturation of Graafian follicles, ovulation, or luteinization of the ruptured follicles. In short, their findings negate the results of other workers in the field and indicate that we are farther than we had hoped from the solution of the physiologic relationships of the anterior hypophysis and that, furthermore, therapeutic attempts with these substances are useless.

In view of these generally negative findings, it may be well for us to examine some of the details of the experiment which may account for this result. At once one is impressed with the age range of the patients who formed the subjects for this experiment. Of the 91 women, 72 were over 35 years of age and 52 were over 40. In other words, over three-fourths of them had entered the last or involutinal phase of reproductive life. This in itself would be meaningless were it not for the fact that we know that the Graafian follicle apparatus is normally more refractory at this time and that failure of maturation and ovulation are extremely common. The authors may be said therefore to have commenced with their experiment weighted somewhat in a negative direction. Had greater success in stimulating the follicle been the result, this weighting would have proved an advantage and made the results all the more convincing; on the other hand, the fact that they failed to evoke ovulation except in two possible instances must be taken with some reserve.

It is true that a cellular response was frequently noted which would indicate that some of the gonadotropic substances had produced growth of thecal and granulosa elements which, though not normal in many respects, were interpreted as the result of definite stimulative properties. Here the matter of control enters in very definitely. The authors studied the ovaries of 25 women who were thought to be normal and used this as a basis for judgment of the abnormal. Because of the care the authors used in arriving at their conclusions, I am inclined to accept the evidence and the conclusions reached and to feel that they have arrived at a very correct result.

All available evidence seems to indicate that the hypophysis excretes gonad-stimulating substances at a constant rate. That is, there is no quantitative cyclical variation. Therefore, why should one suppose that increased amounts introduced by any means would result in increased activity of the ovary? The cyclical variation in the follicular apparatus of the ovary is in all probability not due to variations in gonadotropic stimulators but to variations in some synergistic substance which makes the gonad susceptible, periodically, to the secretions of the anterior lobe. The most likely substance which could have this effect is thyroxin and, as Gunbrecht and Loesser have shown, is in all probability essential to the periodic response of the ovarian elements. I am therefore very sorry that the present authors did not include thyroxin in their list of substances to be tested in combination with the gonadotropes.

This study represents the most complete and thorough study of the effect of gonadotropic substances on the human ovary which has thus far appeared. I feel



## TIME OF ONSET AND DURATION OF THE TOXEMIAS OF LATE PREGNANCY IN RELATION TO THE DEVELOPMENT OF PERMANENT VASCULAR DAMAGE\*

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THE post-partum follow-up of patients who have recently suffered from one of the toxemias of late pregnancy is a relatively new addition to the practice of obstetrics. Formerly it was considered that necessary care ended some fourteen days after delivery. Later, certain individual physicians and clinics requested their patients to return six weeks post partum, but examination at this time was aimed at the detection of pelvic abnormalities resulting from labor rather than the after-effects of the toxemias. In 1924 Harris published a statistical study on a number of toxemic patients examined one year after delivery and found that certain of them evidenced an apparently persistent hypertension at that time. Since then a relatively voluminous literature has been accumulated indicating the frequency with which essential hypertension, chronic nephritis, or as it is now better known, chronic vascular disease follows toxemic pregnancy. Although we have become aware of the frequency with which chronic damage is to be found subsequent to a toxemic episode, many pertinent questions remain unanswered. For example, it is often impossible to state whether the vascular condition antedated the pregnancy or resulted from the toxemia. Indeed it has been suggested that the former is universally the case, but that the abnormal condition of the arterioles had been too slight to be detected previously by any known means of examination. Furthermore, quite frequently, the differential diagnosis between chronic vascular disease and so-called "toxemia of pregnancy" cannot be made during gestation but must await prolonged follow-up study. It has been suggested that the only real aids toward immediate diagnosis are the parity of the patient (chronic vascular damage being observed most frequently in multiparas), careful examination of the eye grounds, and the month of onset of toxemic manifestations.

It has for some time been my opinion that the time element is of importance with regard to the toxemias in two ways: in the first place, in relation to the month of gestation when signs and symptoms appear and, in the second place, in relation to the number of weeks elapsing between their appearance and the termination of pregnancy. In an effort to clarify this dual problem a study has been made of 500 patients observed at the Johns Hopkins Hospital throughout a pregnancy complicated by toxemia, and subsequently followed at intervals of three months for from two to twelve years after delivery. All of these

\*Read by invitation at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

Dr. Novak, I believe, sensed the real significance of the paper. It had two aspects, one a scientific and the other a very practical one. The practical one was to disseminate the idea that all the things one reads in the literature may not be true. A good deal has been written recently about the gonadotropins and much damage has been done, as Dr. Novak emphasized, perhaps not to the patient's well-being but certainly to her pocketbook.

As far as radiation of the pituitary is concerned, I have had no experience with it in human beings in relation to stimulating ovarian function. It might be a very fruitful field for investigation. It is certainly not harmful, and we have used it in the menopause without any untoward results.

TABLE II. PARITY OF PATIENTS IN SERIES ACCORDING TO MONTH OF ONSET OF TOXEMIA

PREVIOUS PREGNANCIES	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.	TOTAL
0	55	85	39	31	12	5	5	232
1 or more	20	58	52	52	29	27	30	268
i	5	20	8	9	9	6	2	59
ii	8	11	11	12	4	5	5	56
iii	1	11	8	10	5	5	9	49
iv	1	6	5	5	3	1	4	25
v	2	5	2	2	2	3	2	18
vi		2	3	6		2	1	14
vii		1	3	1			3	8
viii	1		7	1	3	1		13
ix			2	2		2	2	8
x	1	1	2		2	1	2	9
xi				1	1	1		3
xii			1	2				3
xiii	1	1						2
xiv				1				1
Primiparas	73.33	59.44	42.86	37.35	29.27	15.62	14.29	46.40
Per cent								
Multiparas	26.67	40.56	57.14	62.65	70.73	84.38	85.71	53.60
Per cent								
Mean parity including present pregnancy	1.92	2.16	3.52	3.54	3.66	4.41	4.71	3.05

TABLE III. BLOOD PRESSURE AND ALBUMINURIA AT TIME OF DISCHARGE ACCORDING TO MONTH OF ONSET OF TOXEMIA

	PER CENT OF TOTAL						
	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.
<i>Systolic Pressure</i>							
To 139	94.67	83.81	79.55	76.25	64.11	77.42	60.00
140 and over	5.33	16.19	20.45	23.75	35.89	22.58	40.00
<i>Diastolic Pressure</i>							
To 89	76.00	69.72	54.54	66.25	46.15	70.97	48.57
90 and over	24.00	30.28	45.46	33.75	53.85	29.03	51.43
<i>Albuminuria</i>							
0	84.00	71.13	76.40	65.00	71.79	90.32	80.00
Trace or +	16.00	28.87	23.60	35.00	28.21	9.68	20.00

change from month to month is like that of systolic pressure. It should be noted, however, that for each monthly bracket the percentage of patients with an abnormally high diastolic pressure is greater than that recorded for systolic. The incidence of albuminuria at the time of discharge varied markedly from month to month, but there was no steady change. We have felt for some time that the presence or absence of albumin in the urine is without value as a criterion for the immediate or remote prognosis of a case of toxemia of pregnancy.

*Blood Pressure and Albuminuria Six Weeks Post Partum.*—Table IV has been constructed on the same basis as its predecessor and shows the incidence of hypertension and albuminuria six weeks post partum. Although the incidence of abnormally high blood pressure readings, both systolic and diastolic, is considerably greater at this time than at discharge from the hospital, the same trend of increase is noted as the onset of toxemia extends back into the earlier months of pregnancy.

women were apparently normal when first seen in the prenatal clinic, and for inclusion in this series it was required that a minimum of three dispensary visits be made, during which time the blood pressure was normal, the urine free from albumin, and other signs and symptoms of toxemia absent. A moderate number had evidenced some form of toxemia in a previous pregnancy but apparently had returned entirely to normal during their routine post-partum follow-up.

The 500 cases comprising this study were first separated into several groups according to the lunar month of pregnancy when toxemic manifestations first appeared. Subsequent analyses of these groups follow:

*Time of Onset of Toxemia and Race of Patients.*—Table I indicates the makeup of the series of patients according to the month of onset of toxemia. It will be noted that the numbers decrease as the earlier months of pregnancy are reached. This is due to the fact that relatively few clinic patients reported early enough to satisfy the previously mentioned criterion of three normal dispensary examinations. Although the total number of patients delivered in the hospital was about equally divided as to race, the colored considerably outnumbered the white in this series. This difference has been found to exist whenever studies on the toxemias have been made and apparently represents a true racial effect.

TABLE I. GENERAL MAKE UP OF SERIES OF TOXEMIC PATIENTS STUDIED. MONTH OF ONSET OF TOXEMIA DIVIDED ACCORDING TO RACE OF PATIENT

RACE	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.	TOTAL
White	29	69	32	36	18	16	12	212
Black	46	74	59	47	23	16	23	288
Total	75	143	91	83	41	32	35	500

*Parity of Patients.*—It will be noted from Table II that the number of multiparas in the series was approximately the same as that of primigravidas, the percentage being 53.60 per cent and 46.40, respectively. This table shows very clearly that in primigravidas the tendency for a toxemia to develop increases month by month until term, while conversely in multiparas the opposite is true; indeed, some 85 per cent of the toxemias developing at the fourth or fifth month are in multiparas while in this group the development of this complication late in pregnancy is much less common. Confirmation of this statement appears in the table under "Mean parity" and shows a parous mean of 1.92 in the term group with a steady rise to 4.71 when signs and symptoms appeared as early as the fourth month.

*Blood Pressure and Albuminuria at Discharge.*—In order to demonstrate statistically the incidence of patients whose blood pressure was within normal limits or abnormally high at the time of discharge from the hospital, an arbitrary yardstick of 140 mm. systolic and 90 mm. diastolic was chosen as the level of beginning hypertension. Table III shows a fairly steady increase in systolic hypertension at discharge as the time of onset of the toxemia recedes from term to the earlier months of pregnancy. Thus, when the toxemia manifested itself first at the end of gestation only one patient in twenty left the hospital with a systolic pressure of 140 or above, whereas in the group whose first signs and symptoms began during the fourth month a similarly adduced ratio of two out of five was found to exist. The trend of diastolic

TABLE VI. TOXEMIAS IN PREVIOUS PREGNANCIES IN MULTIPARAS OF SERIES ACCORDING TO MONTH OF ONSET OF TOXEMIA IN PRESENT PREGNANCY

	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.	TOTAL
Total multiparas	20	58	52	52	29	27	30	268
Eclampsia in previous pregnancy	1	1	0	0	3	3	4	12
Other toxemia in previous pregnancy	9	18	23	27	15	15	14	121
Total toxemia in previous pregnancy	10	19	23	27	18	18	18	133
Per cent toxemia in previous pregnancy	50.00	32.76	44.23	51.92	62.07	66.67	60.00	49.62

*Toxemia in Previous Pregnancies.*—Table VI shows that of the total 268 multiparas in the series, 131 or approximately one-half of them had evidenced a toxemia in a previous pregnancy. The incidence of previous toxemia was somewhat less in patients who developed late toxemia (eight months to term) than in those who developed it at an early date (four to seven months).

*Toxemia in Subsequent Pregnancies.*—Of the 500 cases studied in the series, 207 of them were observed in one or more subsequent pregnancies. Of these, 147, or 71.01 per cent, again evinced toxemia, as is shown in Table VII. The incidence of repeated toxemia was lowest in the

TABLE VII. INCIDENCE OF TOXEMIA IN SUBSEQUENT PREGNANCIES ACCORDING TO MONTH OF ONSET OF TOXEMIA IN PRESENT PREGNANCY

	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.	TOTAL
Total patients with subsequent pregnancies	32	63	38	26	19	14	15	207
Total patients with toxemia	9	35	33	23	18	14	15	147
Per cent of patients with toxemia	28.12	55.55	86.84	88.46	94.74	100.00	100.00	71.01

“term” group and rose rapidly. Of those patients whose analyzed toxemia began at the eighth month or less, only 9, or 8 per cent, were observed with a subsequent normal pregnancy.

*Incidence of Chronic Vascular Damage According to Month of Onset of Toxemia.*—Following these statistical summaries of pertinent data accumulated from the 500 cases of toxemia of pregnancy under discussion, we now reach the most significant part of the discussion, namely the end result in terms of chronic vascular damage. In this latter category are included all patients evidencing vascular and renal disease. The vast majority of them were found to have cardiovascular renal disease, a few chronic hemorrhagic nephritis, and there was one instance of apparent nephrosis. As has been said, all of the patients were apparently normal at the onset of the toxemic pregnancy; yet according to Table VIII, 63.40 per cent were ultimately found to show chronic damage. The incidence of this was two and three-quarters times as high in the multiparous as in the primiparous portion of the group. Obviously the future prognosis for the multipara with toxemia is extremely bad, and *when the condition first evidenced itself at the seventh lunar month or earlier no multipara was found on late return to be normal.* The prognosis for the primipara is generally less discouraging unless the first manifestations occur before the last trimester

TABLE IV. BLOOD PRESSURE AND ALBUMINURIA SIX WEEKS POST PARTUM  
ACCORDING TO MONTH OF ONSET OF TOXEMIA

	PER CENT OF TOTAL						
	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.
<i>Systolic Pressure</i>							
To 139	60.42	53.26	28.30	41.17	24.00	35.00	15.00
140 and over	39.58	46.74	71.70	58.83	76.00	65.00	85.00
<i>Diastolic Pressure</i>							
To 89	40.42	53.27	28.30	25.49	24.00	35.00	15.00
90 and over	59.58	46.73	71.70	74.51	76.00	65.00	85.00
<i>Albuminuria</i>							
0	89.54	92.39	90.57	92.16	92.00	95.00	95.00
Trace or +	10.46	7.61	9.43	7.84	8.00	5.00	5.00

Probably the most important item to be noted in this chart is that even six weeks after delivery many patients ultimately found to be normal still evidenced hypertension. Conversely, normal readings were frequently obtained on individuals who later were diagnosed as having chronic vascular disease. The presence of albumin in the urine did not show the above trend, and positive results were obtained more frequently in the higher as contrasted with the lower monthly brackets. Throughout, albuminuria was noted less frequently at the examination six weeks after delivery than at the time of discharge from the hospital.

TABLE V. BLOOD PRESSURE AND ALBUMINURIA TWO TO TEN YEARS AFTER DELIVERY  
ACCORDING TO MONTH OF ONSET OF TOXEMIA

	PER CENT OF TOTAL						
	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.
<i>Systolic Pressure</i>							
To 139	81.33	65.03	32.93	21.68	7.32	0.00	5.71
140 and over	8.67	34.97	67.07	78.32	92.68	100.00	94.29
<i>Diastolic Pressure</i>							
To 89	77.33	66.43	34.07	22.89	12.20	3.13	5.71
90 and over	22.67	33.57	65.93	77.11	87.80	96.87	94.29
<i>Albuminuria</i>							
0	93.33	93.00	85.71	81.93	95.12	90.62	91.43
Trace or +	6.67	7.00	14.29	18.07	4.88	9.38	8.57

*Blood Pressure and Albuminuria Two to Ten Years After Delivery.*—Table V shows the results of examination of the 500 patients two to ten years after delivery. The readings used to make up this chart were the last obtained in the toxemia clinic prior to the time the data for this paper were accumulated (November, 1940). They indicate well the high incidence of chronic hypertension found in a group of patients who, prior to a toxemic pregnancy, were apparently normal in this regard. Furthermore the marked increase in incidence of hypertension as the toxemia manifested itself earlier and earlier in pregnancy, should be noted. Thus when signs and symptoms were found only at term, or during the ninth and eighth month of pregnancy, 40 per cent of the patients were ultimately found to have both systolic and diastolic hypertension, whereas if the onset was during an earlier month 88 per cent were abnormal in this regard. The incidence of albuminuria again varied markedly in the various monthly brackets but no definite trend was found.

From the standpoint of the future, it is unfortunate that so many of the toxemias occurring early in pregnancy run an apparently benign course, and hence gestation is allowed to continue. It is our feeling that the later interests of the patient would often be better served if after a maximum of four weeks' observation the pregnancy were terminated, for it seems entirely possible that such a plan would allow most patients to return completely to normal, when, at a later date, another pregnancy might possibly eventuate without complication.

TABLE X. OUTCOME IN SUBSEQUENT PREGNANCIES ACCORDING TO TIME ELAPSING BETWEEN ONSET OF TOXEMIA AND DELIVERY

WEEKS OF TOXEMIA	TOTAL PATIENTS	TOXEMIA	PER CENT TOXEMIA
1-2	72	32	44.44
3-4	30	16	55.33
5-8	35	31	88.57
9-12	24	22	91.67
13 and over	46	46	100.00
Total	207	147	71.01

*Outcome in Subsequent Pregnancies According to Weeks Elapsing Between Onset and Delivery.*—Table X indicates the outcome to be expected in a subsequent pregnancy according to the number of weeks elapsing between the onset of toxemia and delivery in the pregnancy under study. As has been said, the prognosis is generally bad. However, there appears again a sharp difference in results if the pregnancy is carried on for less than four weeks or for more. In the first group the incidence of chronic vascular damage was 47 per cent as contrasted with 94 per cent in the latter.

*Repeated Toxemia.*—Although possibly not a pertinent part of this study, the following pieces of information were obtained on the remote effects of repeated toxemia and seem worthy of note here:

1. Two hundred and twenty-seven patients were observed who had a toxemia either in a previous or a subsequent pregnancy in addition to the toxemia included in this study. Of these only four, or 1.76 per cent, were apparently normal when last seen.

2. One hundred and thirty-three patients were observed who had had a toxemia in a previous pregnancy. Of these, only three, or 2.26 per cent, were apparently normal when last seen.

3. One hundred and forty-seven patients were observed who had a toxemia in a subsequent pregnancy. Of these, one, or 0.68 per cent, was apparently normal when last seen.

4. Fifty-three patients were observed who had a toxemia both in a previous and a subsequent pregnancy. Of these none remained normal.

#### SUMMARY AND CONCLUSIONS

A statistical analysis has been presented of 500 patients who were followed through pregnancies complicated by toxemia. Although some of these patients had had toxemia in a previous pregnancy, all were apparently normal when first seen during the present one.

The cases were first divided according to the lunar month of onset of toxic signs and symptoms. It was found that the race and age of the patient, the degree of hypertension and amount of albuminuria during pregnancy, the type of delivery and the result to the child, all

of pregnancy, in which case, according to our analysis, chronic vascular damage is relatively certain to follow.

TABLE VIII. INCIDENCE OF CHRONIC VASCULAR DAMAGE ACCORDING TO MONTH OF ONSET OF TOXEMIA

MONTH OF ONSET	PRIMIPARAS			MULTIPARAS			TOTAL PATIENTS		
	TOTAL PA-TIENTS	CHRON-IC VASCU-LAR DAMAGE	PER CENT	TOTAL PA-TIENTS	CHRON-IC VASCU-LAR DAMAGE	PER CENT	TOTAL PA-TIENTS	CHRON-IC VASCU-LAR DAMAGE	PER CENT
Term	55	5	9.09	20	15	75.00	75	20	26.67
9 mo.	85	19	22.35	58	40	68.97	143	59	41.26
8 mo.	39	15	38.46	52	48	92.31	91	63	69.23
7 mo.	31	16	51.61	52	52	100.00	83	68	81.93
6 mo.	12	11	91.67	29	29	100.00	41	40	97.56
5 mo.	5	5	100.00	27	27	100.00	32	32	100.00
4 mo.	5	5	100.00	30	30	100.00	35	35	100.00
Total	232	76	32.76	268	241	89.93	500	317	63.40

TABLE IX. INCIDENCE OF CHRONIC VASCULAR DAMAGE ACCORDING TO TIME ELAPSING BETWEEN ONSET OF TOXEMIA AND DELIVERY

WEEKS OF TOX-EMIA	PRIMIPARAS			MULTIPARAS			TOTAL PATIENTS		
	TOTAL PA-TIENTS	CHRON-IC VASCU-LAR DAMAGE	PER CENT	TOTAL PA-TIENTS	CHRON-IC VASCU-LAR DAMAGE	PER CENT	TOTAL PA-TIENTS	CHRON-IC VASCU-LAR DAMAGE	PER CENT
1-2	115	19	16.52	55	36	65.45	170	55	32.35
3-4	47	9	19.15	35	28	80.00	82	37	45.12
5-6	18	7	38.89	26	25	96.15	44	32	72.73
7-8	11	7	63.64	30	30	100.00	41	37	90.24
9-12	24	17	70.83	39	39	100.00	63	56	88.89
13-16	8	8	100.00	29	29	100.00	37	37	100.00
17-20	4	4	100.00	28	28	100.00	32	32	100.00
21 and over	5	5	100.00	26	26	100.00	31	31	100.00
Total	232	76	32.76	268	241	89.93	500	317	63.40

*Incidence of Chronic Vascular Damage According to Weeks Elapsing Between Onset and Delivery.*—Table IX indicates the late outcome to the patients in the series according to the number of weeks elapsing between the first appearance of signs and symptoms of toxemia and termination of the pregnancy. Although a few instances of apparent postmaturity were noted, in an appreciable number the delivery was premature. This latter group was sometimes spontaneous, but was more often the result of artificial induction of labor or cesarean section. The table shows that in no instance was a primipara with toxemia carried for more than twelve weeks (three lunar months) without chronic damage resulting, while six weeks (one and one-half lunar months) was a similar dividing line in the multiparous group.

It is our opinion that the number of weeks elapsing between the onset of toxemia and delivery is of greater importance in determining the final outcome than the month of onset. As an example, the author has observed a patient who, as a primigravida, developed at the fifth month a toxemia sufficiently severe to require immediate termination of the pregnancy. A year later, after thorough medical study, she was found to be completely free of signs or symptoms of chronic vascular disease.



## INTERPRETATION OF BLOOD PRESSURE BEHAVIOR DURING PREGNANCY AND THE PUERPERIUM\*

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THE discovery that hypertension complicates pregnancy, either early or late in gestation, is rightfully regarded as of serious significance. Since it may indicate either vascular disease or true toxemia, differentiation of these conditions assumes much importance, not only in the management of the pregnancy, but in the final classification and ultimate prognosis of the disorder.

It is our purpose to point out certain observations during pregnancy and the puerperium, which not only aid in interpreting the behavior of the blood pressure, but which enable one to predict that a moderate rise in blood pressure will probably occur in the latter part of pregnancy. It is desired to emphasize, particularly, the value of retinal examination in the differentiation and management of true toxemia and vascular disease, and the importance of examination of the formalin-fixed placenta in the final classification of the disorder.

Assuming the patient presents herself in the first trimester of pregnancy, one may anticipate, even at this early period, a greater likelihood of hypertension of a truly toxic nature, late in pregnancy, if the patient is an adolescent. This fact was noted by us in a previous study<sup>1</sup> and has, no doubt, impressed itself on many observers in the past.

Likewise, if the patient presents certain stigmas of glandular disease, as noted by Vorzeimer and associates,<sup>2</sup> such as disturbance in height-weight ratio, hypothyroidism, pituitary disorder, etc., she is more likely to develop true toxemia of pregnancy.

We have learned to attach great importance to a retinal examination. Early in pregnancy, the arteries are studied particularly for evidence of sclerosis as shown by disturbance in arteriovenous (A-V) ratio, increase in light reflex and occurrence of A-V compressions; late in pregnancy, for evidence of toxemia, as shown by the occurrence of spasms or hemorrhages. In severe toxemia or advanced cardiovascular-renal disease, hemorrhages and whitish exudates may be seen.

The normal relation of the caliber of the artery to that of the vein is 2 to 3, indicating the diameter of the arteries should be two-thirds that of the veins. Arteries of this caliber, being free of sclerosis, do not reflect light and do not compress the vein where the artery may cross it, or cause dilatation of the vein, distal to the point of compression.

For thorough examination of the retina the room should be darkened and the pupils dilated by a mydriatic, such as one drop of 1 per cent homatropine, instilled into each eye, which produces ample dilatation within thirty minutes. Following the examination, the pupils may be quickly constricted to normal size by the use of a miotic, as one drop of

\*Read at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

failed to show significant changes according to the month of onset. The incidence of multiparas in the various groups increased as the time of onset fell back into the earlier months of gestation. If the toxemic condition became manifest near the beginning of gestation, the number of abnormally high blood pressure readings increased, both at the time of the patient's discharge from the hospital and at the six weeks post-partum visit. Even six weeks after delivery many patients ultimately presenting signs of chronic vascular disease had normal blood pressure readings and the converse was also true. In those patients evidencing toxemia early in pregnancy the incidence of previous toxemia was higher than in the group first manifesting abnormality in the later months. A similar trend was noted when an analysis was made according to the outcome of subsequent pregnancies. The incidence of chronic vascular damage was high (63.40 per cent) and was greater among multiparas (89.93 per cent) than primiparas (32.76 per cent). No primipara was seen whose toxemia occurred prior to the sixth month and who remained normal. For the multiparous group the same was true prior to the eighth month.

The series was also divided according to the number of weeks elapsing between the onset of the toxemia and delivery. Here no primipara remained normal who had been carried for more than twelve weeks subsequent to the development of toxemic manifestations. A similar limit of six weeks was found for multiparas. It seems evident that the duration of a toxemia from its beginning to delivery is of more importance from the standpoint of subsequent vascular disease than is the month of onset. Finally, it is believed that termination of the pregnancy in an effort to avoid chronic damage is justified if signs and symptoms persist after four weeks of observation and treatment.

TABLE I. 286 CONSECUTIVE CASES RETINAL EXAMINATION EARLY AND LATE IN PREGNANCY

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(64 per cent below 30 years of age and 86 per cent showing diastolic blood pressure below 70 mm. mercury)	
(A)	239 Cases (83.6 per cent) showed normal A-V ratio (2-3).
(a)	179 Cases (74.9 per cent) maintained normal blood pressure to term. (Diastolic blood pressure not above 80 mm. mercury.)
(b)	60 Cases (25.1 per cent) developed hypertension four to six weeks before term (diastolic above 80 mm. mercury).
(1)	9 Cases (15 per cent) showed apparent change from normal A-V ratio to between 1 to 2 and 2 to 3 during pregnancy—vascular disease?
(2)	22 Cases (36.7 per cent) proved true toxemia (Art. spasms and toxie infarcts).
(3)	29 Cases (48.3 per cent) presumably very mild toxemia (retinal and placental examination either negative or not done).
(B)	47 Cases (16.4 per cent) showed disturbed A-V ratio between 1 to 2 and 2 to 3, occasionally 1 to 2, seldom 1 to 3.
(a)	17 Cases (36.2 per cent) maintained normal blood pressure to term.
(b)	30 Cases (63.8 per cent) developed hypertension four to six weeks before term.
(1)	26 Cases (86.7 per cent) proved vascular disease (absence of Art. spasms and toxie infarcts).
(2)	4 Cases (13.3 per cent) proved true toxemia (presence of Art. spasms and toxie infarcts).

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In other words, if the blood pressure was normal early in pregnancy, but the A-V ratio was slightly disturbed (between 1 to 2, and 2 to 3 or even 1 to 2) approximately *two-thirds* of these cases developed mild to moderate hypertension in the last four to six weeks of pregnancy, in contrast to only *one-fourth* of the cases having normal A-V ratio early in pregnancy. The hypertension in the disturbed ratio group did not exceed 150/95 unless there was a superimposed true toxemia, and was usually not in excess of 135/90. The incidence of true toxemia in the normal A-V ratio group was approximately three times as high as in the disturbed A-V ratio group, the hypertension in the latter being apparently on the basis of vascular disease.

In the above series of cases, the evidence of vascular disease was of a mild degree, yet it was associated with significant elevation of blood pressure and albuminuria in the last four to six weeks of pregnancy. When vascular disease is present to a more severe degree, certain other characteristics serve to differentiate it from true toxemia. It is important, therefore, to contrast the two conditions.

Hypertension, present early in pregnancy or arising later in pregnancy, is interpreted on the basis of vascular disease or true toxemia according to the following behavior and characteristics.

1. If, on retinal examination early in pregnancy, there is evident disturbance in the A-V ratio, varying from 1 to 2 to 2 to 3, or 1 to 2 up to 1 to 3, 1 to 4, or more, it is evident that the pregnancy is complicated by vascular disease. The more marked the disturbance in A-V ratio, the earlier the onset of hypertension in pregnancy and the more marked the increase in light reflex and A-V compressions. Hemorrhages and exudates are usually not seen unless the disturbance is

one-fourth per cent eserine instilled into each eye. No increase of intra-ocular tension has been noted from the use of these drugs over a period of several years.

We have considered 80 mm. of mercury the upper limit of normal diastolic blood pressure during pregnancy and the puerperium and considered any rise above this figure indicative of hypertension. While there is usually a corresponding rise in systolic blood pressure, the latter is subject to more variations and influences and is not so dependable as an index of hypertension. It is rather a measure of the cardiac effort to sustain adequate circulation in the face of increased peripheral resistance. Considering the fact that the majority of diastolic blood pressures is in the range of 60 to 70 mm. of mercury throughout pregnancy (86 per cent in this series), any rise above 80 mm. of mercury is a danger signal, necessitating observation at five- to seven-day intervals to avoid overlooking a rapidly progressing true toxemia.

If, early in pregnancy, one finds a normal A-V ratio of 2 to 3, the blood pressure is almost invariably normal. If hypertension develops late in pregnancy in these cases, it is almost certain to be on the basis of true toxemia of pregnancy, as substantiated by finding toxic types of infarcts in the placenta or sharp spasms in the retinal arteries. In a few instances, however, we have noted the development of a comparable degree of mild hypertension late in pregnancy, apparently on the basis of vascular disease, with a change, during pregnancy, from a normal A-V ratio of 2 to 3 to one between 1 to 2 and 2 to 3. That such a change may occasionally take place during pregnancy, is supported by the fact that A-V ratios between 1 to 2 and 2 to 3 early in pregnancy, occasionally change to 1 to 2 late in pregnancy. Whether this is on the basis of spasm or sclerosis is difficult to determine.

If, early in pregnancy, the A-V ratio is found to be 1 to 2, or between 1 to 2 and 2 to 3, even though the blood pressure is usually normal and continues to be normal month after month, nevertheless, one may predict that a moderate hypertension will occur during the last four to six weeks of pregnancy.

That this behavior of the blood pressure can be predicted and does occur may be seen from an analysis of 286 consecutive cases in which a retinal examination was done early in pregnancy. Table I shows the results of this analysis.

Table I may be summarized in the following statements:

1. In a series of 286 consecutive cases examined early in pregnancy, about one-sixth showed slight to moderate disturbance in A-V ratio, even though the blood pressure at that time, was normal.
2. Of the patients showing normal A-V ratio early in pregnancy, about *one-fourth* developed hypertension four to six weeks before term; the remainder maintained normal blood pressure.
3. Of the cases showing disturbed A-V ratio early in pregnancy, about *two-thirds* developed hypertension four to six weeks before term. About nine-tenths of these were apparently due to vascular disease and showed no serious manifestations.
4. True toxemia, as shown by clinical symptoms, arterial spasms and toxic placental infarcts, was three times as frequent in normal A-V ratio cases as in disturbed A-V ratio cases, developing hypertension late in pregnancy.

harmful effects on her vascular system and liver. In such cases, hypertension and albuminuria usually persist and subsequent observations show the patient has acquired vascular disease. However, it is well recognized that marked hypertension due to fulminating toxemia, subsides quickly after spontaneous or induced labor, and apparently leaves the patient none the worse for the experience.

7. Finally, examination of the formalin-fixed placenta from cases of hypertension due to vascular disease, shows no infarcts of the toxic types, namely the "C," "D," "E" and possibly the "B" types.<sup>3</sup> If infarcts of these types are present, they are proof of the toxic origin of the hypertension.

It is therefore apparent that in examination of the retina and the formalin-fixed placenta, we have the means of more accurate diagnosis and classification of cases of hypertension during pregnancy. If one finds a distinct disturbance in A-V ratio early in pregnancy, he is forewarned of the probability of development of hypertension in the latter part of pregnancy. The extent of the increase and the stage of pregnancy at which it will appear are directly proportionate to the degree of disturbance in the A-V ratio. Examination of the formalin-fixed placenta serves as a check in the final classification of the nature of the hypertension. Type "A" infarct (white) is nontoxic; Type "B" (yellow) is usually associated with slight hypertension and albuminuria; Type "C" (brown yellow) is associated with moderate toxemia; Type "D" (brown) is associated with severe toxemia and Type "E" (black) is associated with acute or fulminating toxemia.<sup>3</sup>

It must be remembered that true toxemia may be so mild that, except for a slightly greater degree of albuminuria and edema, it may simulate the picture above described as due to vascular disease with slight disturbance in A-V ratio. Failure to appreciate the fact that mild vascular disease may simulate mild toxemia in the last six weeks of pregnancy was responsible for the fact that in a former study of "unknown placentas"<sup>3</sup> a majority of the errors was made in this class of cases. The case was judged, clinically, to be one of mild toxemia but was classed as an error since toxic type of infarct was not found. We would now recognize such a case as one of mild vascular disease with the evidence now obtainable by retinal examination.

Briefly, therefore, the development of mild hypertension and albuminuria in the last four to six weeks of pregnancy may be due to (1) mild vascular disease, (2) Type "B" or "C" infarcts, or (3) Type "D" or "E" infarcts. The first two show a slow progression from week to week, whereas the third progresses rapidly, even within a week. Knowledge that the hypertension is on the basis of vascular disease lessens the physician's concern, but should not lessen his watchfulness.

Stander<sup>4</sup> recognized mild cases of albuminuria and hypertension in the latter part of pregnancy, which he classified as "low reserve kidney" rather than true toxemia. This type of case has since been the subject of much controversy, and the trend of opinion by other authors has been to regard these manifestations as indicative of a very mild toxemia. With the evidence obtained by retinal and placental examinations, we feel that these cases should remain in the category of low

severe and of long standing, with associated kidney involvement. Localized arterial spasms are not seen unless there is a superimposed toxemia.

Hypertension due to true toxemia rarely occurs as early as the fifth month but becomes increasingly frequent after the seventh month. The A-V ratio is normal and the arterial spasms, at first sharply localized, become spindle-shaped and elongated with the increasing hypertension until, in severe cases, there is generalized constriction and the A-V ratio becomes much disturbed. Since the disturbed ratio is due to spasm rather than sclerosis, there is no corresponding increase in light reflex or A-V compressions, which helps to rule out vascular disease.

2. Edema, headache, and albuminuria are much less pronounced in vascular disease than in true toxemia with a comparable elevation of blood pressure.

3. Following the initial rise in blood pressure and appearance of albumin, subsequent observations at weekly intervals show very gradual increase in hypertension and albumin in vascular disease from week to week, as compared to true toxemia. Superimposed true toxemia causes rapid increase in edema, headache, hypertension, albuminuria, and the appearance of arterial spasms, the final evidence being found in the placenta as acute placental infarcts.

4. The more severe cases of vascular disease, which occur much more frequently among colored than white women, usually show a striking and unexplainable response to rest in bed. One frequently observes a blood pressure of 180/100 return nearly to normal after several days' rest in bed. An immediate return to the former high level is noted when the patient again resumes the upright position, even though she carries on no physical exertion. These cases also show marked fluctuation in blood pressure from day to day for no apparent reason.

In contrast to this behavior, hypertension due to true toxemia is not much influenced by rest in bed or indeed by any other measures. It remains persistently elevated and tends to increase. Edema may lessen with rest in bed but headache and albuminuria increase. Arterial spasms, at first sharply localized, become spindle-shaped, elongated, and finally produce generalized constriction. Hemorrhages in the retina may occur. Finally, examination of the formalin-fixed placenta shows the acute types of toxic infarcts.

5. The concentration test on the urine and the blood chemistry values are seldom affected in either vascular disease or toxemia of pregnancy, unless advanced cardiorenal disease or severe toxemia have seriously affected the kidneys. However, the uric acid value, which is usually normal in vascular disease, is definitely increased in toxemia, due probably to increased liver damage in the latter.

6. Hypertension and retinal changes due to vascular disease persist throughout the puerperium and show a gradual tendency to increase. This is likewise true of toxemia, if expectant treatment is followed, induction of labor delayed, and the patient subjected to long-continued

in pregnancy, coupled with its continuation in the postnatal period, indicates a profound and sometimes permanent disturbance of the equilibratory apparatus of the vascular system.

A similar, though local, vascular spasm to the point of tissue necrosis has been nicely demonstrated by Dr. Harold Jones and his co-workers, in the menstrual endometrium and also in the decidua of ectopic pregnancy. This local damage is almost surely produced by changes in hormonal balance. It would seem reasonable to me to believe that the general vascular spasm of toxemia may be due to a more profound and lasting glandular imbalance.

Stability of glandular balance may determine the incidence of toxemia, while the ability to readjust the balance, when the disturbance is removed, should determine prognosis post partum and in future pregnancies. Dr. Peekham has shown the course of this readjustment during the period of involution.

Dr. Bartholomew has for years stressed the importance of degenerative changes in the placenta as a cause of toxemias. To me it seems more probable that the changes in the placenta are an additional example of disturbed physiology rather than an etiologic factor.

Yet I agree with Dr. Bartholomew in general that the placenta is probably the cause of toxemia. As soon as the placenta begins to function as a gland of internal secretion, toxemias such as vascular spasm, disturbance in glucose metabolism, in appetite, in water balance, and in glandular activity appear. As soon as the placenta dies or is removed, readjustment begins. Evidence, such as that produced by Drs. Smith, White, and co-workers, suggests that abnormalities in hormonal production, excretion or metabolism are a part of the toxemias of pregnancy.

A summary of these factors would suggest that the sudden impact of the tremendous quantities of hormones produced by this large, new and very active gland of internal secretion, the placenta, produces toxemia in those individuals who are unable to adjust themselves to it. The increased incidence of toxemia in association with the million units of prolan or the high levels of estrin excreted in twenty-four hours by the hydatidiform placenta is corroborative evidence. A considerable number of these unstable individuals are unable completely to readjust balance when the disturbing element is removed by delivery, and the residual scars of toxemia probably result.

**DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.**—The preceding papers contain two important points for consideration, namely: the early examination of the eye grounds in pregnant women as a newer diagnostic as well as a differential diagnostic sign; and a therapeutic suggestion in bringing to our attention the ultimate danger involved in permitting a toxemic woman to continue such a pregnancy over a certain period of time.

Dr. Bartholomew in discussing the arteriovenous ratio in the fundus of the eye may have found the solution to the problem which Dr. Peekham brings up in his paper. This is concerned with the question of whether particular vascular conditions antedate pregnancy. Routine use of the ophthalmoscope early in every pregnancy may throw some light on the further course of that pregnancy.

The examiner of the eye in pregnancy should be especially interested in the significance of changes in the caliber of the vessels. Experience may assist us to distinguish between the arteriolar sclerosis antedating pregnancy and the arteriolar spasm which is a part of the generalized phenomena in the specific toxemia of late pregnancy.

Dr. Peekham has stressed the relationship between the duration of toxemia and the ultimate changes found in the vascular system. In reviewing the histories of some 400 toxemic maternal deaths which occurred in the last ten years in Philadelphia, we obtained information that compared fairly closely with his as far as parity, previous toxemia, and the importance of a high diastolic pressure. In the Philadelphia series, the specific toxemias were most frequent in young primiparas, especially obese women or those with a suggestion of endocrine dysfunction; while the chronic hypertensive lesions appeared more frequently in the older, multiparous women. Over half of our 400 patients who died of toxemia gave a history of

reserve kidney, provided retinal examination shows evidence of vascular disease and placental examination shows no infarcts of the toxic types. This view presupposes that the kidneys show a similar, if not greater, degree of vascular disease.

We therefore venture to predict that when the types and significance of placental infarcts are more generally recognized, and the value of retinal examination in pregnancy is appreciated, there will result not only more uniform statistics concerning pregnancy complicated by toxemia and vascular disease, but more rational management of pregnancy when complicated by these conditions.

#### CONCLUSIONS

1. Examination of the retina and the formalin-fixed placenta are of fundamental importance in the interpretation of blood pressure behavior during pregnancy and the puerperium.

2. *Two-thirds* of patients showing mild to moderate disturbance in A-V ratio of the retinal vessels early in pregnancy, develop mild to moderate hypertension and albuminuria four to six weeks before term.

3. This behavior is on the basis of vascular disease, progresses very slowly and seldom requires interruption of pregnancy.

4. The greater the disturbance in A-V ratio, the more marked the increase in arterial light reflex and A-V compressions, the greater the hypertension and the earlier in pregnancy it arises.

5. Only *one-fourth* of patients showing normal A-V ratio early in pregnancy develop hypertension and albuminuria four to six weeks before term. True toxemia is relatively greater in this group than in the disturbed ratio group.

6. Hypertension, due to vascular disease, is accompanied by less edema, headache, albuminuria and blood uric acid increase and is more responsive to rest in bed than that of true toxemia.

7. Arterial spasms indicate true toxemia, and if found in connection with disturbed A-V ratio, increased light reflex and A-V compression, indicate true toxemia superimposed on vascular disease.

8. Hypertension due to toxic types of placental infarcts may simulate that due to vascular disease but can be differentiated not only by the clinical course but by retinal examination. Final proof rests upon examination of the formalin-fixed placenta.

#### REFERENCES

- (1) Colvin, E. D., and Bartholomew, R. A.: AM. J. OBST. & GYN. 37: 584, 1939. (2) Vorzeimer, J. J., Fishberg, A. M., Langrock, E. G., and Rappaport, E. M.: Ibid. 33: 801, 1937. (3) Bartholomew, R. A., and Colvin, E. D.: Ibid. 36: 909, 1938. (4) Stander, H. J., and Kuder, K.: Ibid. 35: 1, 1938.

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#### DISCUSSION ON PAPERS BY DRS. PECKHAM, BARTHOLOMEW AND COLVIN

DR. EDWARD D. ALLEN, CHICAGO, ILL.—Early recognition of vascular spasm as a prognostic sign should not only aid us in safeguarding our patients prenatally, but, as Dr. Peckham has stressed, should assist in the prognosis of an existent, as well as a future pregnancy. The appearance of recognizable vascular spasm early



cases, likely to have a chronic vascular disease. The concept that we have been using since 1933 is that the patient who can be carried for four weeks or longer with definite evidence of toxemia is, in most instances, a patient with hypertensive disease. We have not been able to carry patients with definite pre-eclampsia for periods of four weeks or longer. Because of the threatening symptoms, we have had to terminate the pregnancy.

Dr. Bartholomew's report that pathologic eye ground findings are present in patients with normal blood pressure is unusual. Furthermore, his statement that a high percentage of these patients subsequently develop hypertension is important. If confirmed, it gives us another test, in addition to the cold pressor test, to detect those patients who may develop toxemia.

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—Dr. Bartholomew presented a list of the criteria which he believes help to separate the chronic vascular diseases from true toxemia. I want to report to you one additional criterion, based on a group of kidney function tests that we have been applying to the toxemia problem at New York University. These are renal clearance tests but made with special substances, one of which, inulin, measures glomerular filtration, while the other, diodrast, is a measure of renal blood flow. Tests of kidney function with these substances indicate striking differences in the patients with true toxemia and those with essential hypertension.

Nonpregnant patients with essential hypertension subjected to these renal clearance tests show signs of having a diminished renal blood flow and probably a constriction of the efferent arteriole to the glomerulus. A study of the patients with pre-existing hypertension in pregnancy indicates that in general these patients follow the pattern that is found in nonpregnant patients. On the other hand, those that develop symptoms only in the last trimester of pregnancy, i.e., patients with specific toxemia or pre-eclampsia, give no evidence of diminished blood flow, but perhaps some diminution in the rate of glomerular filtration. Later, after delivery, if these toxemic patients develop a persistent hypertension, then the kidney function tests are identical with those of essential hypertension in nonpregnant women or in men.

Dr. Peckham opened an interesting question when he said that, in regard to ultimate prognosis, the duration of time during which the patient suffered from toxemia was more important than the period of pregnancy at which these symptoms appeared. Now there are two concepts of the relationship of toxemia of pregnancy to hypertension. According to one view the toxemia is a special response of an already predisposed patient to the usual strains of pregnancy; according to the other there is a true toxemic process developing only during pregnancy and producing the damage to kidney and blood vessels that results in permanent hypertension. It seems to me that if specific toxemia were simply the development of symptoms on the basis of a pre-existing disposition to vascular disease, then the person with the greatest predisposition would exhibit this symptom earliest in pregnancy, so that the time of onset would be of most importance in ultimate prognosis. On the other hand, if the subsequent hypertension were due to damage resulting from an acute toxic process, then the duration of time during which the patient's organs were subject to these toxic effects would be most important in determining the probability of later chronic hypertension. Dr. Peckham's results seem to me to support the latter concept, and I am anxious to hear whether he believes this also.

DR. PECKHAM (closing).—I am still completely at a loss as to whether chronic vascular damage develops in patients previously susceptible to this condition or whether the process results from the toxemia itself. Many people have made vigorous attempts to prove that in those individuals later showing chronic vascular damage a subliminal condition was previously present but had not been diagnosed. However, so far as the studies which I have observed are concerned, it has seemed to me that in most instances, excepting those patients with obvious vascular disease antedating pregnancy, an arteriolar spasm develops and if that spasm is carried on over a certain period of time actual sclerosis results due to interference with the vascular supply of the vessels themselves. In other words, I am inclined to feel that chronic damage is the result of so-called pregnancy toxemia rather than a pre-existing disease.

previous toxemia, stillbirth, or repeated abortions. In a large number of the cases, the fatal outcome followed too long an attempt to carry the fetus to a viable period.

From his conclusions, a toxemic pregnancy should not be permitted to continue longer than four weeks if we are to avoid subsequent vascular damage. In many instances a choice will have to be made by the family between a possible live baby and a subsequently damaged woman with a necessarily shorter expectancy of life. From his findings the point may be raised as to whether the majority of toxemic women should be sterilized at or subsequent to the time of delivery.

With premarital physical examinations and evidence of negative syphilis an essential for marriage in many States, it seems to me that we have an excellent opportunity to determine the fitness of many women for reproduction. With pre-conceptional examinations including eye grounds, we may be able to determine and warn patients who are poor risks against the dangerous strain of a pregnancy.

DR. ROBERT D. MUSSEY, ROCHESTER, MINN. (by invitation).—The incidence of recognized toxemia of pregnancy among the obstetric patients at the Mayo Clinic has been about 5 per cent. Fifty-seven per cent of those patients, who had one or more subsequent pregnancies, had recurrence of the toxemia. It is evident that in many of these cases there were unrecognized vascular changes.

The hypertension of the toxemias of pregnancy is on the basis of vascular spasm in the presence of a toxic factor in the circulating blood. There seems to be direct ratio between the degree of hypertension, which indicates the severity of toxemia, the length of time this toxemia is imposed on the vessels, and the extent of degenerative vascular injury and of ensuing chronic cardiovascular-renal disease. High blood pressure is not, however, necessarily followed by vascular injury, since hypertension from hyperthyroidism, for example, is not commonly followed by vascular damage.

In cases of acute toxemia, spastic and other changes in the retinal arterioles furnish a valuable index of the degree of injury to the general vascular system. Repeated examinations reveal the rate at which this injury progresses. The presence and extent of changes in the retinal vessels may thus be helpful in determining if and when to terminate pregnancy.

When the patient is seen for the first time in the latter part of pregnancy, and has a mild elevation of blood pressure, it is sometimes difficult to determine whether the slight narrowing of the vessels, referred to by the authors, indicates previous vascular disease or a manifestation of the vasospasm accompanying early toxemia. Routine examination of the retinal vessels in the early months of pregnancy would undoubtedly establish a better basis on which to judge changes which may occur when the patient is examined later or when hypertension is present.

DR. J. HOFBAUER, CINCINNATI, OHIO (by invitation).—The recorded experimental and biochemical data warrant the conclusion that the various manifestations of pre-eclampsia bear a close resemblance to the morbid state produced by vasopressin (Byrom, Knepper, Gollwitz). The natural secretion of vasopressin may reach toxic levels if inadequately opposed by a pitressin-inhibitory substance. The existence of an inhibitor was surmised by Byrom, Teel, and Page.

I believe that acetylcholine, which is found in a considerable quantity in the normal human placenta (Dale, Gaddum, Hauptstein, Loeschke) and which acts as a powerful vasodilator, is a balancing force, designed to restrain forces favoring vascular hypertonia. Hyperfunction of the endocrine glands (thyroid, adrenal cortex, anterior pituitary), abundance of sex hormones in the blood, and the impairment of the excretory function of the liver represent the factors augmenting vascular tone.

Our findings of low levels of acetylcholine and increased levels of acetylcholine esterase in placentas of patients with severe toxemia and notably low choline values in the blood of pre-eclamptic and eclamptic patients point to a derangement of placental function. This placental deficiency is probably related to placental acute infarction and autolysis.

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—Dr. Peckham states that if the toxemia lasts for four weeks or longer the patient is, in the vast majority of

## ENDOCRINE FACTORS IN SECONDARY AMENORRHEA\*†

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THE numerous factors responsible for the occurrence of secondary amenorrhea have made it very difficult to develop practical clinical classifications and to determine correct therapeutic indications. It is desirable, therefore, to accumulate as many data as possible from these patients in the hope that they may eventually yield the necessary information. For this purpose our report is based on a statistical analysis of certain observations made on 73 selected clinic patients in whom no clear-cut cause for the disturbance could be found. The features studied consisted of (1) age, (2) duration of amenorrhea, (3) past history, (4) menarcheal age, (5) previous menstrual history, (6) fertility, (7) body weight, (8) basal metabolic rate, (9) assays of estrogenic and gonadotropic hormones in the blood, and (10) prognosis in an untreated group.

Many of the causes of secondary amenorrhea are found in definite organic lesions, such as tumors of the anterior hypophysis, adrenal cortex, or ovaries, or are associated with clinical entities, for example, tuberculosis, diabetes mellitus, severe malnutrition, psychic disorders. In most of the other cases it has been said that a differentiation usually may be made according to the endocrine gland chiefly involved and they are grouped under such diagnoses as primary or secondary anterior hypophyseal, adrenal, or ovarian failure. This method of approach is laudable and is practicable when the findings leave no doubt, but in most patients seen by the gynecologist the evidences of the endocrine disorder are variable and uncertain and demand both imagination and a rare diagnostic acumen for an unquestionable verdict.

The 73 patients of our series represent a selected group in whom the exact etiologic factor could not be determined in spite of careful clinical and laboratory investigation, and for that reason we believe that they are sufficiently homogeneous to allow a general comparison of the various points we have studied. This report is considered as a preliminary review of the series as a whole, and it is hoped in the future to correlate more closely the findings in the different groups.

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Our thanks are due to Dr. Horace Gray for his assistance with some of the mathematical analyses used in this study.

DR. BARTHOLOMEW (closing).—In studying these cases of mild vascular disease developing hypertension late in pregnancy, we wondered whether they fell into the class that Dr. Stander called low reserve kidney. They do conform to that class as far as mildness of the symptoms is concerned. He found, however, that cases classed as low reserve kidney did not tend to recur, whereas many cases in our series did manifest the same behavior in subsequent pregnancies.

Whether one regards the placental infarcts as the cause or the effect, they are nevertheless very consistently associated with toxemia of pregnancy. When one finds the acute or subacute types of placental infarcts, the case must be regarded as one of true toxemia. If vascular disease is also present, toxemia is superimposed, and is an independent condition.

## THE MENARCHE

The statement frequently has been made that a delayed onset of the menses is often found in women with oligomenorrhea and secondary amenorrhea. In order to determine this point the age at the menarche of the patients of this series has been compared with those of a group of normal Californian women. This control series is composed of 154 obstetric patients observed in our clinic in 1931 (Hotelling<sup>1</sup>). The actual figures are given in Table I.

TABLE I. FREQUENCY DISTRIBUTION OF THE MENARCHEAL AGE OF 73 PATIENTS WITH SECONDARY AMENORRHEA AND A CONTROL GROUP OF 154 NORMAL WOMEN

AGE (CENTRAL)	CONTROLS		AMENORRHEA	
	NUMBER	PER CENT	NUMBER	PER CENT
9.5	0	0	1	1
10.5	3	2	1	1
11.5	12	8	10	14
12.5	15	10	8	11
13.5	59	38	17	24
14.5	27	17	21	29
15.5	19	12	3	4
16.5	13	8	10	14
17.5	3	2	1	1
18.5	3	2	1	1
Total	154	100	73	100

The information used in studying both groups was obtained from the patients' statements and consequently is open to error, but nevertheless they are considered comparable. Since women generally give the "age at last birthday" when asked for their "age at the first menses" the half-year mark was used arbitrarily as the true point in computing the figures. When the different classes of the controls were plotted, the curve showed a normal Gaussian distribution, with the mean at 14.039 years, the standard deviation 1.593, and the standard error of the mean 0.128. The mean of the amenorrhea group was 13.925 years, slightly earlier than the controls, but the difference 0.115 years or 32 days is not considered as significant.

It may be stated, therefore, that in our series of patients with secondary amenorrhea no evidence was found to support the contention that such patients as compared to a normal group are more likely to give a history of a delayed appearance of the menarche.

## PREVIOUS MENSTRUAL HISTORY

In contrast to the normal range of the menarcheal age found in this series is the large percentage of the subjects who complained of various menstrual disorders preceding the onset of the present illness (Table II). Since the records are necessarily based on the patients' recollections and not on carefully kept menstrual calendars, the actual figures are open to many errors.\* Nevertheless, the trend is clearly discernible, since a

\*When figures are obtained from case histories, as in this study, they cannot be compared with careful calendar records made by school girls, college students, or nurses such as have been published in recent years. Instead, they must be applied to data obtained in the same manner by interrogation of patients. For example, 27, or 18 per cent, of 154 obstetric patients on the Stanford service stated that they had "irregular menses" (Hotelling<sup>1</sup>), but a careful analysis of calendar records kept by a group of 76 nurses in the same institution showed an incidence of "irregular menses" of 63 per cent (Fluhmann<sup>2</sup>).

## AGE

The patients selected were less than 35 years of age at the time their menses ceased, and in every instance at least one year had elapsed following the menarche. It was hoped in this way to avoid the inclusion of problems peculiar to early menstrual life and the premature appearance of the menopause. The range was from fifteen to thirty-eight years when estimated according to the age at the time of the first visit to the clinic, and from fifteen to thirty-five years when considered from the age of onset of the amenorrhea. The distribution was as follows:

AGE	FIRST VISIT	ONSET AMENORRHEA
15 to 19	12 cases	15 cases
20 to 24	18 cases	20 cases
25 to 29	25 cases	22 cases
30 to 35	15 cases	16 cases
35 to 38	3 cases	

## DURATION OF AMENORRHEA

The duration of the amenorrhea varied from six weeks to ten years, this information being obtained from the patients' statements at their first visit. Since most of them were subsequently observed for periods of a few weeks to several months without menstruating, the actual duration was considerably longer in most instances. Some of the cases also should be considered as representing "oligomenorrhea" or "recurring periods of amenorrhea," and they have been included in order to give the correct perspective to our analysis of the preceding menstrual history. For the sake of convenience they may be subdivided into 5 categories, according to the length of the amenorrheic period:

6 weeks to 10 weeks	13 cases
11 weeks to 18 weeks	19 cases
19 weeks to 30 weeks	17 cases
7½ months to 18 months	13 cases
1½ years to 10 years	11 cases

## PAST HISTORY

In selecting the patients for this series, a number were excluded because of acute or chronic illnesses which often are associated directly or indirectly with the occurrence of amenorrhea. We eliminated instances of pulmonary tuberculosis, diabetes mellitus, pituitary adenoma, chlorosis, tuberculosis of the spine, cephalothoracic lipodystrophy, rigid diet for reducing, amenorrhea subsequent to mumps, and ovarian arrhenoblastoma. Among those included, however, were 2 patients in whom the period of amenorrhea had its onset following abortion and in 5 instances of long duration it followed a full-term pregnancy. In addition, it is of interest that 11, or 15 per cent, of the group gave a history of a previous pelvic operation, although the relationship of this fact to the incidence of secondary amenorrhea is not clear. In 4 cases the operation consisted of a unilateral salpingo-oophorectomy, and there were one instance each of appendectomy and unilateral salpingectomy, tubal sterilization, appendectomy and suspension of the uterus, bilateral salpingectomy, cesarean section, cesarean section and tubal sterilization, and one of an unknown nature but which was not a bilateral oophorectomy or hysterectomy.

these had had no pregnancies, 27 had had one or more full-term pregnancies, and 4 had had one or two spontaneous abortions. Of the 19 with no pregnancies, it is known that 16 were married for from eleven months to fifteen years, used no contraceptives, and the majority mentioned sterility as a complaint when they came under our care. If this figure is taken as a minimum, it may be said that sterility occurred in 32 per cent or more of the whole group. Since the incidence of infertile marriages in the population at large is estimated at about 15 or 16 per cent, a low fertility was present in this series twice as often as in normal individuals. This finding is in keeping with Rubin's reported observations of women with oligomenorrhea and hypomenorrhea.<sup>3</sup>

#### BODY WEIGHT

It long has been recognized that extremes of body weight are important clinical accompaniments of secondary amenorrhea. In this series, the height and weight of 66 patients are known, and they have been compared with normal standard estimates obtained from the Medico-Aetuarial Insurance Table.<sup>4</sup> For further study and comparison we selected a control group consisting of 100 women in the same age categories, with no gross pelvic disease and complaining of menorrhagia, metrorrhagia, polymenorrhea, dysmenorrhea, sterility, or habitual abortion (Table IV).

TABLE IV. FREQUENCY DISTRIBUTION OF INDEX OF BODY WEIGHT OF A SERIES OF 66 PATIENTS WITH SECONDARY AMENORRHEA AND A GROUP OF 100 CONTROLS

INDEX WEIGHT OBSERVED WEIGHT PREDICTED $\times 100$	CONTROL SERIES	AMENORRHEA	
		NUMBER	PER CENT
200-204		1	1.5
195-199			
190-194		2	3.0
185-189		1	1.5
180-184			
175-179		2	3.0
170-174			
165-169			
160-164		1	1.5
155-159			
150-154	1		
145-149		1	1.5
140-144		1	1.5
135-139	2	3	5.0
130-134	2	4	6.0
125-129	1	3	5.0
120-124	1	2	3.0
115-119	5	5	7.0
110-114	9	4	6.0
105-109	8	4	6.0
100-104	7	4	6.0
95- 99	9	3	5.0
90- 94	18	8	12.0
85- 89	7	7	10.0
80- 84	17	3	5.0
75- 79	10	4	6.0
70- 74	2	2	3.0
65- 69	1	1	1.5
Total	100	66	100

TABLE II. PREVIOUS MENSTRUAL HISTORY OF 73 PATIENTS WITH SECONDARY AMENORRHEA

I. Normal menses prior to amenorrhea	19
Except one previous period of amenorrhea (6 months or more)	4
Total	23
II. Menstrual disorder present since menarche	29
Oligomenorrhea	15
Oligomenorrhea and hypomenorrhea	4
Oligomenorrhea and hypermenorrhea	6
Polymenorrhea	1
Irregular menses, then hypomenorrhea	1
Oligomenorrhea and hypomenorrhea, and at least one previous long period of amenorrhea	2
III. Menstrual disorder for varying periods before onset of present amenorrhea	21
Oligomenorrhea	6
Oligomenorrhea and hypomenorrhea	9
Oligomenorrhea and hypermenorrhea	1
Hypermenorrhea	1
Hypomenorrhea	2
Oligo- or hypomenorrhea and one previous long period of amenorrhea	2

history of "normal, regular menses" was obtained in only 23 of the 73 subjects (32 per cent), and in 4 there had been at least one previous period of amenorrhea. In 50 (68 per cent) instances there was a history of some previous menstrual disorder, usually irregular delayed menses with or without hypomenorrhea or hypermenorrhea. In 29 subjects (39 per cent) the disturbance had been present since the menarche, while in 21 (29 per cent) it appeared for periods varying from a few months to several years before the onset of amenorrhea.

### FERTILITY

It is obviously beyond the scope of this report to study in detail the obstetric history of the patients and its relation to the occurrence of amenorrhea, but Table III shows that, as a whole, they represent a "low fertility" group. Fifty of the 73 women were married, and 19 of

TABLE III. PREVIOUS OBSTETRIC HISTORY OF 73 WOMEN WITH SECONDARY AMENORRHEA

Not married*	23
Married	50
No pregnancies	19
Married 11 months to 15 years	16
Length of marriage not known	2
Contraceptives	1
Full-term pregnancies†	27
Gravida i, Para i	9
Gravida ii, Para i	5
Gravida ii, Para ii	4
Gravida iii, Para ii	2
Gravida ii to vi, Para i to iv	5
Gravida i, Para i, sterilized	1
Gravida ii, Para ii, sterilized	1
Incomplete pregnancies	4
Gravida i, Para 0	3
Gravida ii, Para 0	1

\*One patient had a previous induced abortion.

†Includes one patient, a nulligravida at the time of observation, who later had three pregnancies.



Although it is not possible in this report to deal in detail with the treatment of patients with secondary amenorrhea, the results obtained in a group receiving solely thyroid extract by mouth is worthy of mention since it is strikingly in accord with the experiences of the authors mentioned in the preceding paragraph. Of 21 patients in this category, all of whom had low basal metabolic rates, 14 responded with regular cyclic bleeding, 1 became pregnant, 1 had a single period of bleeding while under observation, 4 remained amenorrheic, while 1 was not followed. It may be stated, therefore, that a so-called "cure" occurred in 15, or 71 per cent, of these patients, a result unequalled in other groups by any other means of therapy we have employed.

#### ESTROGENIC HORMONES IN THE BLOOD

The employment of tests for estrogenic hormones in the blood and urine of women with various disturbances of the menstrual cycle once gave hope that they might offer much assistance from the standpoint of diagnosis as well as therapy. Several extensive studies have been published, notably by Frank and his associates,<sup>7</sup> Siebke,<sup>8</sup> Mazer and Goldstein,<sup>9</sup> Fluhmann,<sup>10</sup> and Albrieux.<sup>11</sup> In each case the authors were able to classify amenorrheic patients according to the estrogen content of blood or urine, but these results have not received any interpretation that lends itself to practical application. They do not differentiate any definite endocrine entities and do not point to effective methods of treatment with available hormonal substances.

The estrogenic hormone content of the blood of 52 patients of our series was determined by the Fluhmann mucification test.<sup>10, 12</sup> The blood was examined weekly for from three to six successive weeks, and, as reported previously before this Society (Fluhmann<sup>10</sup>), the patients could be divided, according to results, into 3 categories. First was the so-called "cyclic" group in whom the level of estrogenic hormones reached a high or comparatively high concentration at intervals of two weeks or more. Second, repeated examinations of the blood showed a constant appreciable amount of the hormones from week to week. Third, estrogens were not demonstrable in the blood during the total period of investigation.

A periodic increase of the blood hormone was observed in 46 of the 52 patients studied, while repeated positive tests were noted in 4 instances and consistent negative results in only two. An analysis of the two smaller groups did not point to any specific individual characteristic or endocrine type associated with the endocrine behavior. This fact and the realization that cyclic estrogen curves also have been demonstrated by our procedure in castrate and postmenopausal women make us feel that this method of investigation does not offer any assistance in the care of women with secondary amenorrhea.

#### ANTERIOR LOBE GONADOTROPIN IN THE BLOOD

The demonstration of an excessive amount of anterior hypophyseal gonadotropic hormone in the blood long has been recognized as evidence of a total loss of ovarian function (Fluhmann<sup>13</sup>), and it is surprising that positive tests were obtained in only 7, or 20 per cent, of 34 patients of this series. This figure is in marked contrast to the occurrence of positive tests in from 65 to 80 per cent of women following castration

The weights in each series were computed for the Index =  $\frac{\text{Weight observed}}{\text{Weight predicted}} \times 100$ . According to this calculation, a normal person should have an index of 100 and any number above this is an indication of overweight. A mathematical analysis of the figures shows that they are statistically significant and that there is a definite tendency toward obesity in amenorrheic women. The average for the control group was 96 and for the amenorrheic women 112. The index for 38, or 58 per cent, of the total number of women with amenorrhea was over 100 and a further glance at the table shows that 10 per cent of them were heavier than the heaviest of the controls with other menstrual disorders or sterility.\*

#### BASAL METABOLIC RATE

One or more records of the basal metabolic rate in 66 of the 73 patients are available, and they support the contention of Haines and Mussey,<sup>5</sup> Litzenberg and Carey,<sup>6</sup> Frank and others,<sup>7</sup> that a lowered thyroid activity is often associated with diminished ovarian function. The range was between minus 27 and plus 21 per cent, so that no great extremes were observed, and there were no definite clinical instances of myxedema or hyperthyroidism. The rate varied within the normal range of plus 10 and minus 10 in 33, or 50 per cent, of the cases, while only 4, or 6 per cent, were more than plus 10, and 29, or 44 per cent, were below minus 10. These figures may be compared with those of 100 women in the same age categories, with no gross pelvic lesions and complaining of sterility, polymenorrhea, menorrhagia, metrorrhagia, or dysmenorrhea. In 58 (58 per cent) of this group the basal metabolic rate was between plus 10 and minus 10; in 12 (12 per cent) it was above plus 10; and it was between minus 10 and minus 24 in only 30 instances (30 per cent) (Table V).

TABLE V. FREQUENCY DISTRIBUTION OF THE BASAL METABOLIC RATE OF 66 PATIENTS WITH SECONDARY AMENORRHEA AND A GROUP OF 100 CONTROLS

BASAL METABOLIC RATE	CONTROL SERIES	AMENORRHEA	
		NUMBER	PER CENT
+21 to +19	0	1	1.5
+18 to +16	4	1	1.5
+15 to +13	1	0	0.0
+12 to +10	7	2	3.0
+ 9 to + 7	6	3	4.5
+ 6 to + 4	9	7	10.5
+ 3 to + 1	7	2	3.0
0	1	2	3.0
- 1 to - 3	12	7	10.5
- 4 to - 6	10	7	10.5
- 7 to - 9	13	5	8.0
-10 to -12	12	10	15.0
-13 to -15	10	7	11.0
-16 to -18	6	6	9.0
-19 to -21	1	2	3.0
-22 to -24	1	1	1.5
-25 to -27	0	3	4.5
Total	100	66	100

\*In this study no allowance was made for hereditary influence. A more detailed analysis of body weight in a group of this type would necessitate serious consideration of racial factors. An appreciable proportion of the patients from the Stanford Clinic trace their origin to peoples bordering on the Mediterranean, and it is well recognized that their women comparatively early gain weight, with or without menstrual disorders.

A definite tendency to obesity was observed, since 38, or 58 per cent, of 66 patients were above the normal standard estimates of the Medico-Actuarial Insurance Table.

No clear-cut instances of marked hypo- or hyperthyroidism were included, but a basal metabolic rate of between minus 10 and minus 27 per cent was found in 29, or 44 per cent, of 66 cases.

The estrogenic hormone content of the blood was determined at weekly intervals in 52 patients. A cyclic increase in the hormone concentration was observed in 46 cases, while repeated positive tests were noted in 4 instances and consistent negative results in only two.

An excessive amount of anterior pituitary gonadotropin was present in the blood of 7, or 20 per cent, of 34 women. It is felt that this observation is evidence of a serious or prolonged ovarian disturbance.

A period of uterine bleeding appeared before any treatment had been instituted in 7, or 33 per cent, of a group of 22 patients.

#### REFERENCES

- (1) *Hotelling, Mrs. Floy*: Personal communication. (2) *Fluhmann, C. F.*: AM. J. OBST. & GYNEC. 27: 73, 1934. (3) *Rubin, I.*: Ibid. 18: 603, 1929. (4) Medico-Actuarial Mortality Investigation, Vol. I, New York, pp. 38 and 67, 1912. (5) *Haines, S. F., and Mussey, R. D.*: J. A. M. A. 105: 557, 1935. (6) *Litzenberg, J. C., and Carey, J. B.*: AM. J. OBST. & GYNEC. 17: 550, 1929. (7) *Frank, R. T., Goldberger, M. A., Salmon, U. J., and Felshin, G.*: J. A. M. A. 109: 1863, 1937. (8) *Siebkke, H.*: Zentralbl. f. Gynäk. 53: 2450, 1929. (9) *Mazer, C., and Goldstein, L.*: Clinical Endocrinology of the Female, Philadelphia, 1932, W. B. Saunders Company. (10) *Fluhmann, C. F.*: AM. J. OBST. & GYNEC. 32: 612, 1936. (11) *Albrieux, A. S.*: Archivos de la Clinica e Instituto de Endocrinologia 1: Part II, p. 805, 1941. (12) *Fluhmann, C. F.*: Endocrinology 18: 705, 1934. (13) *Idem*: J. A. M. A. 93: 672, 1929.

STANFORD UNIVERSITY HOSPITAL

#### DISCUSSION

DR. HAROLD O. JONES, CHICAGO, ILL.—In interpreting his own work Dr. Fluhmann has made several pertinent, straightforward statements which should command the attention of all clinicians. He states:

1. That the estrogen content of the blood or urine does not differentiate any definite entities.

2. That quantitative determinations of the estrogen content in the blood or urine do not offer any assistance in the care of women with secondary amenorrhea. (These two statements, based on the work of several years, immediately gain favor, since it is obvious that the authors would be most desirous of attaching clinical significance to their experimental findings.)

3. That spontaneous cures in patients with secondary amenorrhea are frequent.

4. That thyroid therapy has been more beneficial than any of the other hormonal substances.

The quantity of anterior lobe gonadotropins in the blood seems to be significant in the differentiation between partial and more complete cessation of ovarian function. This, if borne out by histologic study of human ovaries, offers a test of clinical value.

My own observations of patients with secondary amenorrhea are in accord with the statement that the cycles in these patients prior to the onset of amenorrhea were not normal in the majority of instances. The balance between functional bleeding, irregular cycles, and amenorrhea is indeed a very delicate one.

There are several known facts that cause blood and urine assays to be of doubtful significance. The amount of sex hormones in the circulating blood is low. This is due to the fact that the liver has a tremendous ability to remove the hormones and change them to substances of very low or no potency. The methods of extracting these hormones from the blood have been very inefficient in the past. The blood

or the menopause. We also have noted the presence of unduly great amounts of this hormone in the blood of 5 out of 6 patients with primary amenorrhea.

Although it is not possible to draw conclusions from so few cases, an analysis of the 7 patients with positive tests indicates that the demonstration of an unduly large amount of anterior lobe gonadotropin in the blood should be considered as evidence of a serious or prolonged ovarian disturbance. As compared to the whole series they represent an older group, the youngest being 25 years of age. The period of amenorrhea was longer than seven and one-half months in all cases, and in 3 instances it was of three, four, and nine years, respectively. Five of the 7 patients had a lowered basal metabolic rate, two a delayed menarche (sixteen and seventeen years, respectively), and 3 were obese. Six of the 7 received treatment, but only 2 responded with cyclic uterine bleeding.

#### PROGNOSIS IN UNTREATED CASES

It is not the purpose of this report to discuss the therapy of secondary amenorrhea, but it is of interest to note the experience of 22 patients in this series who were under observation for some weeks or months and yet received no treatment. In 15 instances there was no change in the amenorrheic condition, but in 4 cases there occurred a single period of bleeding following which the patients failed to report, and 3 women experienced a return of cyclic uterine bleeding. Of these 7, only 2 had periods of amenorrhea of less than three months' duration and could be considered as merely examples of *oligomenorrhea* in whom an early reappearance of the menses could be expected, while in two the condition had been present for four and five years, respectively.

Any estimation of therapeutic measures employed in secondary amenorrhea must take into consideration that there is a certain incidence of spontaneous "cures." In this series 7, or 35 per cent, of a group of 22 patients had a period of uterine bleeding while they were under observation and before any treatment had been instituted.

#### SUMMARY

This report is based on 73 clinic patients with a secondary amenorrhea for which no definite cause could be ascertained.

The age of the patients varied from fifteen to thirty-eight years at the time of observation, and the duration of the amenorrhea from six weeks to ten years.

Amenorrhea set in after an abortion in 2 instances and after a full-term pregnancy in 5 cases. Eleven, or 15 per cent, gave a history of a previous pelvic operation.

The range and the mean of the menarcheal age showed no significant difference from a control group of normal women.

A preceding menstrual disorder, most often oligomenorrhea or hypomenorrhea, was noted in 50, or 68 per cent, of the whole group. In 29, or 39 per cent, the disturbance had been present since the menarche and in 21, or 29 per cent, it appeared for varying periods immediately preceding the amenorrhea.

Infertile marriages were present in over 30 per cent of the married women in the group.

balance. In a number of instances, with or without treatment, I have observed a cyclic tendency, characterized by alternating phases of functional bleeding and amenorrhea, over a term of years.

The real indication for treatment in a large proportion of cases is an associated sterility, especially as the amenorrhea in itself is harmless to the patient. On the other hand, we encounter an interesting group in which pregnancy occurs even when amenorrhea has been present for long periods of time, even a good many years. In such cases a typical endometrial cycle occurs, except for the bleeding phase. There is a curious lack of knowledge as to the histology of the endometrium in such cases, although it seems likely that the transition between the progestational and the postmenstrual stages is brought about by a simple involutional change, and is not associated with desquamation or bleeding.

DR. SAMUEL H. GEIST, NEW YORK, N. Y.—I would like to ask Dr. Fluhmann whether there was any correlation between the gonadotropic hormone findings and the estrogen findings?

DR. JENNINGS C. LITZENBERG, MINNEAPOLIS, MINN.—It is nineteen years since I promulgated the idea that basal metabolism was an important factor in all complications of menstruation. My first report in 1926 was only preliminary, but it is with considerable satisfaction that I note in Dr. Fluhmann's group reported today that the low basal metabolism figures agreed with mine almost exactly.

DR. FLUHMAN (closing).—I should have made it clear that this report is merely a preliminary study. When we started this work, it was our hope that the findings in the different groups could be correlated and possibly give us a clue to some sort of classification. However, the problem became far too complicated, and we offer these statistics now merely as observed facts.

Dr. Pratt's question with regard to hypothyroidism is a very embarrassing one, and I do not know just what to say. Certainly some of the patients were overweight and had a low basal metabolic rate. We decided finally to include them, but we eliminated individuals who were definitely myxedematous.

The question of diet was carefully considered, and no patient was included in whom there was definite evidence of malnutrition.

Two of the patients with excessive amounts of anterior pituitary gonadotropin in the blood also presented a cyclic rise in estrogenic substances.

The injection of estrogenic substances directly into the cervix uteri, which a discussant mentioned, is not a new procedure. It must be employed with caution and is not devoid of risks. The question came up recently during the course of a trial in California, and the doctor concerned was suspected of attempting to produce an abortion by means of such injections.

has not been hydrolyzed, and thus 30 per cent, or less, of the hormone has been recovered for assay. Due to the small number of animals used in the assays of such material, the percentage of error ranges from 100 to 10,000.

DR. JEAN PAUL PRATT, DETROIT, MICH.—In selecting clinical patients in whom no clear-cut cause for the disturbance could be found, one may question whether hypothyroidism has been excluded by the authors. In Table V, 73 per cent of the patients had a minus basal metabolic rate. In Table IV, 57.5 per cent of the patients were overweight. To what extent do these variations in the basal metabolic rate and weight coincide? Furthermore, 71 per cent of the patients with low basal metabolic rate were relieved of amenorrhea by the administration of thyroid. Other reports are cited showing that a lowered thyroid activity is often associated with diminished ovarian function. To eliminate known causes of amenorrhea, would it have been desirable to test the response to thyroid therapy in all the patients in this group? What symptoms are necessary to establish a diagnosis of mild hypothyroidism?

Would it be desirable to include diet in the investigation of the causes of secondary amenorrhea? Extreme malnutrition was assumed as an obvious cause of amenorrhea. Is it possible that lack of balance of proteins, carbohydrates, and fats, as well as a deficiency in vitamins, might be important factors though extreme variations in the apparent state of nutrition were not conspicuous?

It has been my practice for several years, when investigating menstrual disorders, to obtain from the patients an accurate record of the food ingested. These data are collected by giving each patient a form to complete. This form includes one column for the kind of food eaten and another for the amount. The patient is requested to continue her customary habits of eating and to complete a form each day for one week. From this information a dietitian computes the number of calories of fats, carbohydrates, and proteins, and estimates the vitamins. Conforming to the individual's taste, a few changes are suggested to restore a normal balance. By this means alone many menstrual disorders may be corrected.

The finding of so many (68 per cent) who complained of various menstrual disorders preceding the onset of the present illness, opens an important though difficult subject for further study. The story of progress in combatting disease usually follows a definite pattern: recognition of the conspicuous manifestations; observation of the less conspicuous symptoms; search for the cause of early symptoms; education of the profession; education of the laity to seek advice for the early symptoms and prevention. Increasing evidence tends to relate secondary amenorrhea to causes operating earlier and manifesting themselves by various menstrual disorders. One may even go further and suggest the relation of menstrual disorders to conditions existing before the menarche. Prevention may belong in the realm of the pediatrician. Gynecologists still have the problem of clarifying the causes of minor menstrual disorders and preventing them.

DR. EMIL NOVAK, BALTIMORE, MD.—It is refreshing to hear a man of Dr. Fluhmann's experience in this field present a paper stressing the limitations rather than the accomplishments in the management of amenorrhea.

As regards the amenorrhea due to defective nutrition, it has always seemed to me that these cases are in the final analysis due to ovarian hypofunction, for the ovaries are singularly sensitive to nutritional deficiencies. The mere withdrawal of certain vitamin principles from the diet of experimental animals, for instance, brings about an abolition of the cycle.

In the present state of our knowledge, no one can feel satisfied with efforts to classify the causes of this disorder. For practical purposes, however, we should try to distinguish etiologic groups as best we can, with full appreciation of the frequently unscientific basis for such division into pituitary, ovarian, thyroid, and other groups.

An interesting variety of amenorrhea is that seen at times following full-term delivery or miscarriage. Pregnancy is one of the critical periods in a woman's endocrine career, and it not infrequently involves a re-shuffle of endocrine factors. Functional bleeding rather frequently has its inception following pregnancy, while in other cases amenorrhea may develop. This is the so-called superinvolutional amenorrhea of the older gynecologists. Many women have an unsteady endocrine

In the entire series, the diagnosis of syphilis as made from the roentgenogram was confirmed by the finding of the organisms of syphilis in 91.5 per cent. There should have been but 1.6 per cent of incorrect

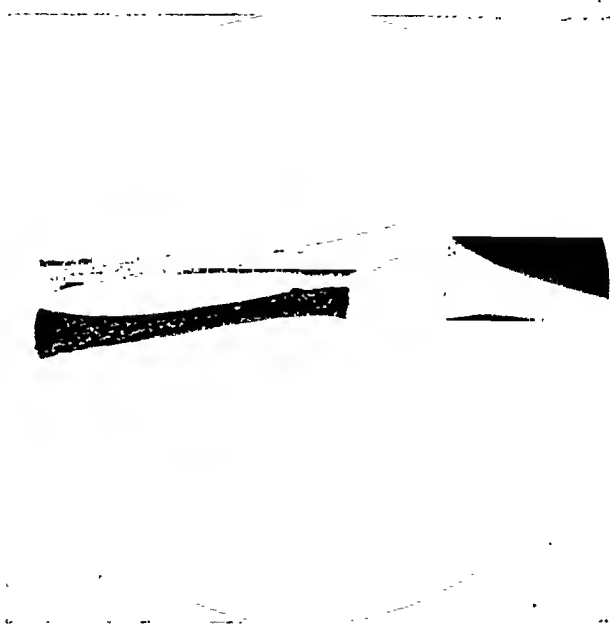


Fig. 1.—Abortion (1,070 Gm.), macerated; Wassermann and Kahn, 4-plus; no treatment; diagnosis, doubtful; organisms found. Probably not safe for average doctor to make diagnosis of so early a lesion.



Fig. 2.—Abortion (610 Gm.), macerated; Wassermann and Kahn, 4-plus; no treatment; diagnosis, syphilis; organisms found. Probably as early a lesion as safe for average doctor to make positive diagnosis.

diagnoses. A review of the 11 films incorrectly diagnosed showed that 9 did not have the serrations or saw-tooth metaphyses upon which premise the study originated (Table I). One erroneous diagnosis was hazardous

## OSTEOCHONDRITIS IN THE STILLBORN\*

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School of Medicine)

CERTAIN skeletal changes in the fetus and newborn as seen by the roentgenogram are almost pathognomonic of congenital syphilis. When deviations that are not typical are called syphilis, this excellent method of diagnosis is discredited. Briefly, what are these typical changes? McLean, in one of his classical articles, says:

"There is a more advanced stage of the previous lesion (rarefaction) in which the roentgenologist can usually make an unequivocal diagnosis of osseous syphilis in the presence of negative serology and a history of a negative physical examination. The so-called zigzag or saw-tooth metaphysis type is not uncommon. Saw-tooth metaphyses are the first evidence of lawlessness of growth so characteristic of the active stage of syphilis, concerning which there has been so much controversy." As long as we make the diagnosis of syphilis upon such lesions we are on safe ground. To quote McLean again: "One should be warned against accepting the presence of one or possibly two minute spurs or buds shown on the metaphyses by the x-rays as evidence of syphilis, since they also occur in rickets. *True syphilitic types show a definite saw-tooth edge.*" (Italics mine.) Failure to heed the above was the cause of most of my failures. Caffey in a recent article says:

"In this non-syphilitic group no cases resembling the following *rarer* [italics mine] types of syphilitic osteochondritis were found: (1) saw-tooth metaphyses; (2) foci of rarefaction in the angles of the cartilage shaft junctions and multiple infarctions through the ends of the shafts."

Evans in a recent communication says: "... and there is no doubt that characteristic osseous lesions are found in a very high percentage of cases of fully developed syphilis. The diagnosis in the less obvious cases is more difficult and both positive and negative errors may be made."

In attempting to prove my point, I desire to present an analysis of roentgen ray studies on 129 negro fetuses at all stages of gestation, the great majority of them stillborn. The work has been done without an experienced and advanced radiologic or histologic background. It is an effort to show that the average doctor can confidently make the diagnosis of advanced congenital syphilis provided he does not split hairs in evaluating the lesions observed. The method of study follows: The diagnosis was made from the film without any knowledge of the case. If the films showed a positive or doubtful diagnosis, the babies were autopsied. The following tissues were stained by the Levaditi method: kidney, liver, spleen, lung, heart and thymus. The bone lesions were reported as syphilitic only when the organisms of syphilis were found in the stained tissues. The original Levaditi stain was used. It is essential that the method be meticulously followed. As an example, we failed to demonstrate the organisms when neutral formalin was used in the place of acid formalin.

\*Read at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.





Fig. 5.—Premature (2,120 Gm.), macerated; Wassermann, 4-plus; no treatment; diagnosis, syphilis, organisms found; pathognomonic saw-tooth serrations, premise upon which this work was done.

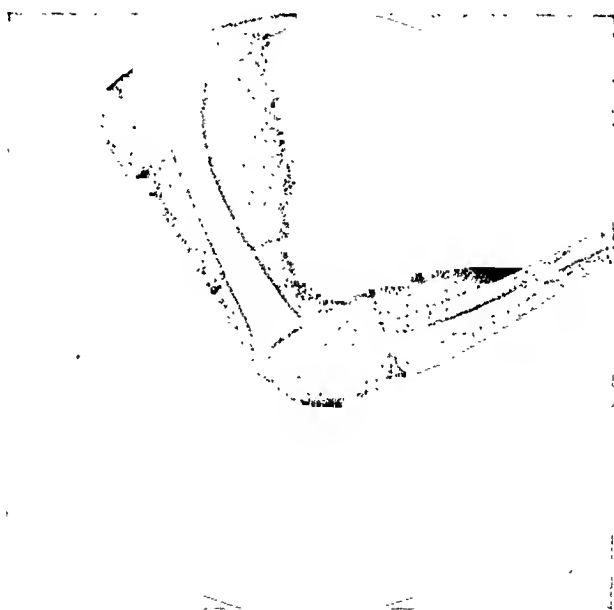


Fig. 6.—Abortion (400 Gm.); Wassermann and Kahn, negative; no treatment; diagnosis, developmental; organisms not found; minute spurs and buds not a safe diagnosis for a fetus of this size.

TABLE II. DIAGNOSES MISSED (11)

Wassermann-Kahn positive	2
Wassermann-Kahn negative	6
Tests agree	8
Wassermann positive	1
Kahn negative	2
Treated	2
Average weight (Gm.)	816
Serology positive	27%

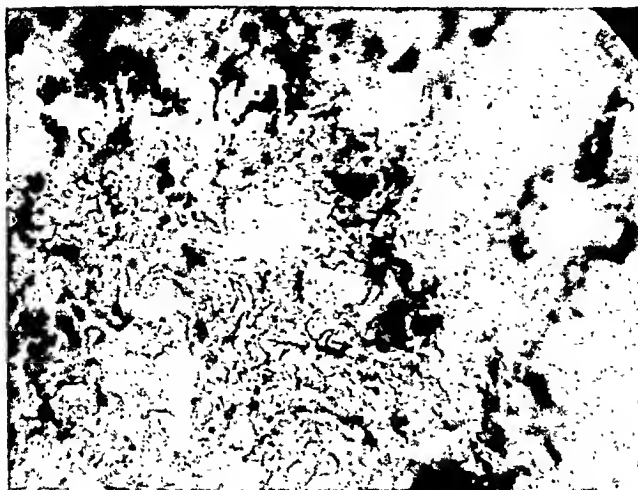


Fig. 3.—Innumerable organisms found in baby of comparatively early lesion of Fig. 2.



Fig. 4.—Term (2,820 Gm.), macerated; Wassermann and Kahn, 4-plus; no treatment; diagnosis, syphilis, organisms found. Comparatively early lesion, probably unsafe diagnosis for average doctor.

TABLE I. REVIEW OF MISSED DIAGNOSES

1. No serrations; plainly neg.	380 Gm.
2. No serrations; plainly neg.	400 Gm.
3. No serrations; plainly neg.	200 Gm.
4. No serrations; plainly neg.	1,400 Gm.
5. No serrations; plainly neg.	1,800 Gm.
6. No serrations; plainly neg.	2,030 Gm.
7. No serrations; plainly neg.	1,050 Gm.
8. No serrations; plainly neg.	240 Gm.
9. Confusing; again positive	600 Gm.
10. Confusing; not typical serrations	560 Gm.
11. Hazardous diagnosis; small fetus	320 Gm.

fetal weight was 1,704 Gm. Only 16 of the women had received any treatment during pregnancy and the average number of treatments was two (Table III).

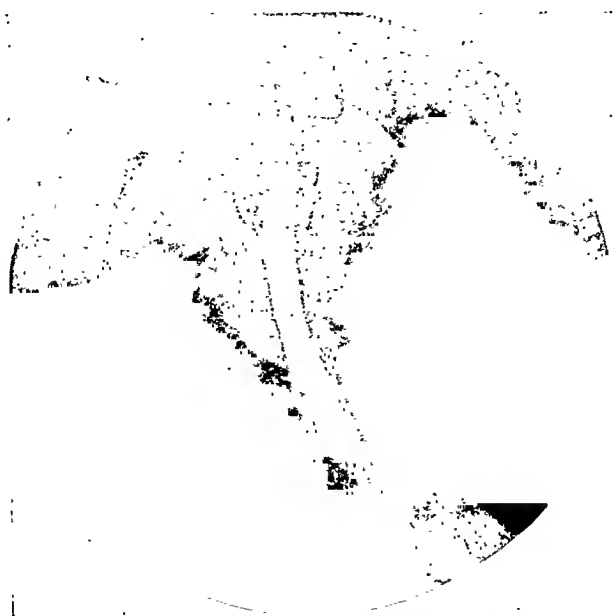


Fig. 9.—Abortion (890 Gm.), macerated; Wassermann and Kahn, 4-plus; no treatment; advanced lesion; organisms found.



Fig. 10.—Premature (2,290 Gm.), stillborn, macerated; Wassermann and Kahn, 4-plus; diagnosis, syphilis; no treatment; organism found; serration, rarefaction, and periosteal elevation.

To compare the serology percentage, 321 negative films were reviewed. Maternal serology was negative in 80 per cent. Fourteen per cent were positive and the mothers received treatment during pregnancy. The average number of treatments was 8.3. Six per cent were positive with

in that the fetus weighed only 320 Gm. In only one was the lesion apparently typical and the organisms not found. Serology was positive in only 27 per cent of the mothers in this group. The average fetal weight was 816 Gm.



Fig. 7.

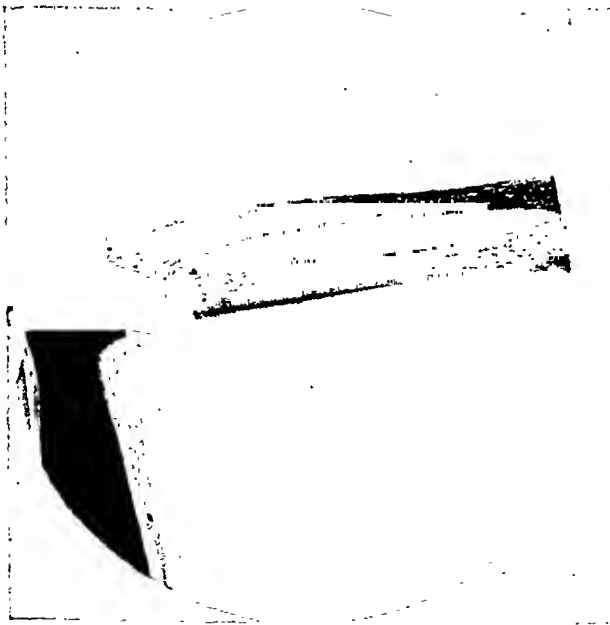


Fig. 8.

Figs. 7 and 8.—Premature (1,520 Gm.), not macerated; Kahn, 4-plus; no treatment; diagnosis, syphilis; organisms not found, even though lesions apparently far advanced.

The diagnosis of syphilis was made from 88 films and the organisms of the disease were found in the babies. The outstanding fact in this group is that 94 per cent of the mothers had positive serology. The average

Nine diagnoses were doubtful. The typical serrations were not present. In two the organisms of syphilis were found, and the maternal serology was positive in 33.3 per cent. Only two mothers received any ante-partum treatment. The average fetal weight was 1,754 Gm.



Fig. 12.—Aged 16, premature (1,500 Gm.), alive; Wassermann and Kahn, 4-plus; no treatment; diagnosis, syphilis; organisms found. Rather rare lesion probably pathognomonic.



Fig. 13.—Other bones of same baby as in Fig. 12.

#### CONCLUSIONS

1. Typical saw-tooth serrations are pathognomonic of congenital syphilis.

2. Properly done Wassermann and Kahn tests should be positive in probably 90 per cent of the mothers of syphilitic babies.

no treatment. It seems justifiable to think that caution should be exercised in diagnosing congenital syphilis of the bones when the maternal serology is negative.

The serologic tests used were: a 3 tube Kolmer modification with serum dilutions of 0.05 and  $\frac{1}{10}$ , with icebox fixation and the standard Kahn. Both of these tests were done upon 76 mothers. There were only 3 discrepancies. It seems probable that this speaks well for the reliability of the tests during pregnancy.

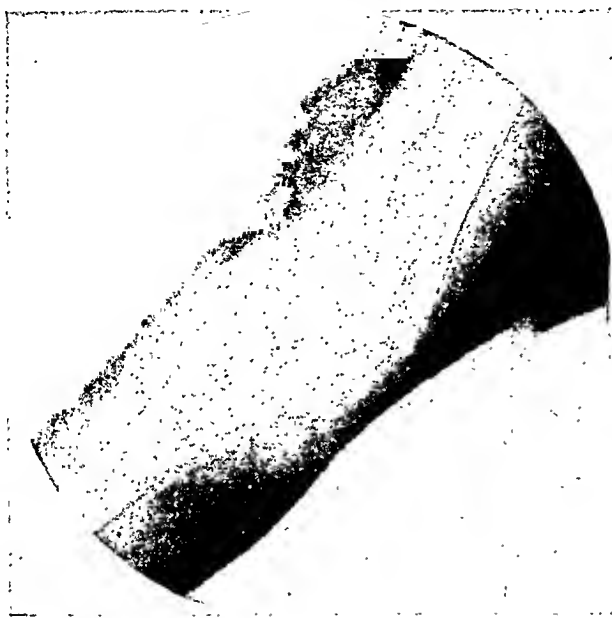


Fig. 11.—Rickets with periosteal elevation.

Twenty fetuses were so small that a diagnosis was not attempted. Their average weight was 229 Gm. The tissues were stained and the organisms of syphilis were not found in any of them. The maternal serology in this group was positive in 35 per cent. The average duration of pregnancy was approximately eighteen to twenty weeks. It is probable that an abortion happened in some of these women before intrauterine infection occurred. It is not wise to attempt the diagnosis of skeletal syphilis on fetuses of this size.

TABLE III. ORGANISMS FOUND

Number studied	88
Wassermann-Kahn positive	47
Wassermann-Kahn negative	3
Tests disagree	3
(Wassermann neg.—Kahn pos.)	
Wassermann positive	27
Wassermann negative	2
Kahn positive	6
Serology positive (%)	94
Treated	16
Average number treatments	2
Average weight (Gm.)	1,704

opened, we have had exactly two stillbirths due to syphilis. I attribute this to the extraordinarily efficient manner in which the local Health Board and the profession handle the local venereal problem.

A great many of our syphilitic women go to term. Many of them give birth to living, full-term children and in that type of infant it becomes necessary to use every possible means either to establish a diagnosis of syphilis or to exclude it. I find the radiographic method very valuable, but I have seen pictures of more syphilitic bones this morning than I have in the last fourteen years.

Practically always the cord Wassermann corresponds to the maternal Wassermann. A 4-plus cord Wassermann will be found in the infant born to the mother who shows a 4-plus Wassermann. If the baby does not have syphilis, the positive Wassermann will become negative in the course of some weeks, whereas if it is a congenital syphilitic, the Wassermann will remain positive.

3. It can be said, rather arbitrarily, that it is unwise to diagnose congenital syphilis by the roentgen ray in fetuses weighing less than 500 Gm.

#### REFERENCES

(1) *Pendergrass, E. P., and Bromer, R. S.*: Am. J. Roentgenol. 22: 1, 1929. (2) *Dennie and Pakula*: Congenital Syphilis, Philadelphia, 1940, Lea & Febiger.

50 ARMSTRONG STREET

#### DISCUSSION

DR. GRANDISON D. ROYSTON, St. Louis, Mo.—It is generally recognized that syphilis and nephritis must be excluded or recognized as a cause in every stillbirth. It is further recognized that routine serologic tests are indicated as early as possible in every pregnant woman, while autopsies on all stillbirths are highly desirable. Yet often the autopsy reports of "autolysis of tissues," negative serologic reactions, etc., are discouraging. Dr. McCord's report denotes that the roentgenograms are the simplest means of diagnosing syphilis as the cause of fetal death.

Serologic reactions of cord blood are of doubtful value since the latter may carry complement fixation antibodies from the mother. These so-called "reagens" may disappear in from one to twelve weeks after birth, when the child's true status may be determined. Roberts believes if the infant reaches the age of four months without positive blood tests or physical evidence of the disease, it probably is not syphilitic. Jeans and Cooke have never found syphilis in an infant with no physical evidence of syphilis, whose Wassermann was negative at two months of age.

The qualitative Wassermann reaction on cord blood is of only minimal importance, but the quantitative determination of titer and comparison with subsequent blood tests seems of greater value. Placental study is of no importance if the mother has received treatment, for even inadequate treatment usually renders the placenta free from evidence of syphilis. I agree with the essayist in preferring the standard Kahn to the Wassermann test.

More than twenty-seven years ago, Ludwig Pick taught that osteochondritis of the long bones was pathognomonic of syphilis, yet it has been too frequently overlooked. Stokes reported that among more than 200 patients with syphilitic bone lesions, only 24 per cent had had serologic tests, while 82 per cent were found to be positive on examination. He emphasizes the necessity of skillful interpretation of the roentgenograms. Syphilis is a preponderantly constructive osteoplastic process, followed later by destructive changes.

Osteochondritis or periostitis in the syphilitic infant is limited to the first five months of the baby's life. It is usually observed at birth or during the first two or three months of life. It is important to remember that syphilitic bone lesions are always bilateral in the first months of life. According to Shands, the order of frequency of these lesions is: (1) the lower ends of the femur; (2) lower ends of the tibia and fibula; and (3) lower ends of the radius and ulna.

The cases of congenital bone syphilis in the St. Louis Children's Hospital from 1920 to 1938 were reviewed by Jostes and Roche of the Orthopedic Department. It is interesting to see that in their series of 34 cases, they found the tibia and fibula involved more than twice as often as the femur.

In the Washington University Clinic, among the last 8,571 obstetric admissions, 6,227 white and 2,344 negroes, 2.8 per cent of the white patients and 14.5 per cent of the negroes were syphilitic. The general incidence of pregnancy and syphilis was 6 per cent. Only 5.8 per cent of these women gave any history of a primary or a secondary lesion.

Among more than 500 infants born of syphilitic mothers, Soule found only two infants with undoubted syphilis, after they had had a *negative cord blood reaction at birth*. This result is due to the fact that practically all of our syphilitic patients are closely supervised for the greater part of pregnancy and receive some treatment.

DR. KARL M. WILSON, ROCHESTER, N. Y.—My material is quite different evidently from that of Dr. McCord and Dr. Royston, since we see very little acute syphilis in my clinic. As a matter of fact, in the fourteen years since the clinic



when nitrous oxide was used, there were actually fewer apneic or asphyxiated babies in the group receiving nitrous oxide than in the group receiving ether. Only two babies out of twenty failed to breathe immediately when nitrous oxide was used as compared with 7 out of 21 when ether was used in comparable types of delivery. This would suggest that the oxygen tension in the blood might not bear the significant relationship to asphyxia that we have supposed.

In view of the existing controversy and the many different opinions, we also undertook a study of the problem. Our purpose was to determine in rabbits, the effect of various analgesic and anesthetic agents on the maternal blood oxygen and carbon dioxide content, the fetal blood oxygen and carbon dioxide content in utero and finally to study microscopically the brains of fetuses delivered from animals subjected to these agents. This report details our experiences with sodium pentobarbital and nitrous oxide.

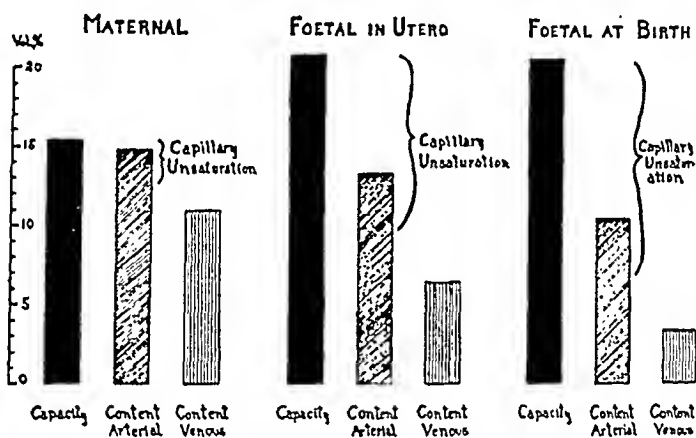


Fig. 1.—Chart showing oxygen relationships of maternal and fetal bloods.

#### METHODS

For the microscopie study of the fetal brains, the pregnant rabbits were given the sodium pentobarbital or nitrous oxide during the last few days of their pregnancy. The time of administration of the anesthetic agent prior to delivery varied from one to ten days. Early in the study we found that if the anesthesia was given too near to the time of delivery the animal would not care for her young.

Sodium pentobarbital was given to the rabbits intravenously. The initial dose was from 0.1 to 0.3 Gm. (1.5 to 4.5 gr.). In some rabbits, this dose was repeated one to three times in order to maintain a constant deep surgical anesthesia for from one to six hours. Our rabbits varied in weight from 8 to 11 pounds, and this dose when compared with clinical doses used in obstetrics would appear very large. For purposes of this study, however, it was felt that such intense dosage was desirable. The animals were allowed to deliver at term. One fetus was killed at birth and the brain carefully removed intact, examined grossly, and prepared for section. Thereafter one fetus was killed each week and the brains studied in a similar manner in order to determine whether any changes had taken place. The brains from

## A STUDY OF INTRAUTERINE OXYGEN EXCHANGE\*

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OBSTETRIC analgesia and anesthesia has been a controversial subject for many years. While it is generally agreed that some control of pain is desirable, some have attempted to carry this to the point of complete relief. Studies made on patients so relieved have pointed toward both immediate and remote detrimental effects on the fetus.

Schreiber,<sup>1</sup> in 1940, suggested that the use of analgesics and anesthetics in obstetrics may sufficiently alter the maternal blood gases to cause marked decrease in fetal blood oxygen with resultant brain injury due to cerebral anoxia in utero. He points out that if the anoxia persists for even a short period of time the tissue changes may be irreparable and that while the child may survive it is likely to develop neurologic changes later in life. While he admits that other factors must be considered in the production of such anoxia, he places particular emphasis upon the role of analgesic and anesthetic agents used in obstetrics.

Reported studies on maternal and fetal blood gases have revealed certain important data.

Eastman<sup>2</sup> showed that the arterial blood going to the fetus in utero was approximately 50 per cent saturated with oxygen at birth while the maternal arterial blood was usually 95 per cent saturated (Fig. 1). He concluded that: "The very high unsaturation of fetal blood in respect to oxygen indicates that the full-term fetus in utero exists normally in a state of cyanosis," and also "Viewed by adult standards the blood reaching fetal tissues is low in oxygen but for needs of the fetal organism it is evidently adequate." He also suggested that the high oxygen capacity, or hemoglobin content of fetal blood is an adaptive or acclimatization phenomenon due to the low oxygen tension to which the fetal blood in the capillaries is subjected, a tension that is estimated at less than 40 mm. of mercury. Steele and Windler<sup>3</sup> reported similar findings in blood studies on animals and demonstrated that the fetal blood gases fluctuated markedly with muscular work on the part of the mother and that uterine contractions and relaxation sometimes markedly reduced the blood oxygen content.

Recently Smith<sup>4</sup> pointed out that with certain anesthetic agents, notably nitrous oxide, the maternal and fetal blood oxygen levels were reduced, and suggested possible fetal injury because of it. Study of his report, however, reveals that, although the oxygen levels were lower

\*Read, by invitation, at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

TABLE II. PRENATAL ANESTHESIA WITH SODIUM PENTOBARBITAL

NO.	DATE OF TERM	DAYS BEFORE TERM	DURATION OF ANESTHESIA	DOSE 1 GR. PER C.C.	MATERNAL VENOUS BLOOD				FETAL SAGITTAL SINUS BLOOD			
					OXYGEN		CARBON DIOXIDE		OXYGEN		CARBON DIOXIDE	
					BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
2	10/11 1/5	4 1	0 1 hr.	0 1.5	10.5 15.1 14.6	56.5 12.8	56.5 52.6 50.5	48.6	0.9 1.8 2.4	0.3 0.8	69.7 54.1 55.7	67.1 60.9
1	10/10 11/24	5 4 4	3 hr. 2 hr. 1 hr.	3.0 2.0 1.5	8.5 13.7 8.6	7.6 13.4 10.5	44.3 49.1 52.9	51.0 54.1 42.9		2.7	45.5	51.2 40.3
5	12/11 1/12	8 2	1 1/4 hr. 1 hr.	1.5 1.5	11.4	11.1 12.3	55.0	58.6 57.3	3.6	1.2	44.8	60.8
7	11/1	1	1 1/4 hr.	1.5								
4	10/20	5 3	3 1/4 hr. 2 1/4 hr.	4.75 2.0	15.6	11.5	32.7	40.6				
8	10/31	9 3	1 hr. 5 1/4 hr.	1.5 2.5	13.3	12.6	35.0	56.8				
12	11/15	10	1 1/2 hr.	2.5	14.3 11.6	6.9	33.6 51.1	54.4				
14	11/17	3	2 1/4 hr.	3.0								
18	12/4	6	1 1/4 hr.	2.5	19.2 20.8	8.9	43.4 52.1	46.4				
		1 0	2 1/2 hr. 1 hr.	2.7 1.5	10.6		28.6		2.6	1.7	56.0	52.6 50.6
16	11/26	7	2 hr.	2.5	10.4 11.3	10.5	49.0 46.0	49.4				
20	12/15	0	1 hr.	1.5	9.9	10.8 8.7	42.1 52.2	42.0		1.8 0.3 0.3	62.0	65.8 61.6 68.2
9	11/1	7	5 1/4 hr.	3.0	15.1	14.6 8.2 5.3	31.8 52.8 39.4	38.0 39.0	0.3 0.6	1.2 0.2 0.3	74.4 78.6	82.1 77.9 77.3
10	1/6	2	1 1/2 hr.	1.5	10.0							
15	11/1	8	1 hr.	2.2	14.3							
	12/17	2	1 hr.	1.5	8.1 8.0	9.0	55.5 58.2	56.7	0.45 0.15	0.3	76.5 74.3	58.3 59.7
	Average				12.5	10.3	45.9	49.2	1.4	0.8	62.8	62.3
	Standard deviation				3.3	2.3	8.8	6.7	1.1	0.6	11.7	9.6

several fetuses removed at the time of cesarean section under sodium pentobarbital were also studied.

In using nitrous oxide the gas was administered to pregnant rabbits approximately the same interval before term as in the sodium pentobarbital experiment. The anesthetic was administered by an experienced anesthetist by a semi-open flow system with a rebreather in the circuit. A small tight-fitting mask was used. A mixture of 90 per cent nitrous oxide and 10 per cent oxygen was given for one-half hour. The animals were allowed to deliver and the brains of fetuses were studied in a manner similar to that described for the sodium pentobarbital-treated animals.

The brains were carefully studied both grossly and microscopically by Dr. Konstantin Sharenberg, Assistant Professor and Pathologist at the Neuropsychiatric Institute of the University of Michigan. To date 58 brains have been examined (Table I). In none could any evidence of gross or cytologic abnormality be seen. The control brains were identical in all respects with those delivered from the anesthetized animals. The changes usually ascribed to cerebral anoxia consist of focal necrosis with loss of cellular outline and nuclear structure but no changes even remotely suggesting these changes were observed.

TABLE I. FETAL BRAINS EXAMINED GROSSLY AND BY MICROSCOPIC SECTION

SODIUM PENTOBARBITAL ANESTHESIA		N <sub>2</sub> O 90% + O <sub>2</sub> 10% ANESTHESIA		CONTROLS	
At birth	12	At birth	11	At birth	3
At 1 week	5	At 1 week	6	At 1 week	2
At 2 weeks	4	At 2 weeks	5	At 2 weeks	2
At 3 weeks	2	At 3 weeks	2	At 3 weeks	1
At 4 weeks	0	At 4 weeks	1	At 4 weeks	1
At 5 weeks	0	At 5 weeks	1	At 5 weeks	0
Total	23		26		9

While it was not possible to attempt behavior studies on the rabbits, it may be said that these animals exhibited normal habits and growth rates when compared with others in the laboratory. In addition, we are privileged to report on an unpublished work carried out in the Department of Psychology by Mr. Stewart Armitage, in which rats born of mothers to whom sodium pentobarbital was given during the latter part of their pregnancies were tested for intelligence by the maze technique established by Dr. Norman Maier. It has been found that these animals showed an ability to solve the maze equal to that of the normal controls.

The study of the maternal and fetal blood gases was carried out as follows:

Under local anesthesia the uterus was exposed through a small incision at or within a few days of term. Maternal and fetal blood samples were obtained under oil within a few minutes of each other. In order to avoid disturbing placental circulation or fetal environment, one fetus was brought under the opening in the abdominal wall, and, without opening the uterus, a needle was inserted through the uterus into the fontanel of the fetus. In this manner, we were usually able

to obtain from 0.4 to 0.8 c.c. of blood from each fetus. In some it was obvious that the specimen contained spinal fluid or brain tissue, and these were discarded. All satisfactory specimens were analyzed by Van Slyke-Neill<sup>5</sup> technique. It was impossible to obtain a specimen of arterial blood from the fetuses.

Most of the maternal specimens were obtained from the ear. In some animals arterial specimens could not be obtained. In others venous blood was obtained from the uterine vein, and in these it was discovered that the  $O_2$  and  $CO_2$  content was essentially the same as the findings recorded for blood obtained from the ear. One specimen was obtained from the mother and from one fetus before the anesthetic agent was given. The dose of sodium pentobarbital was the same as used for studies on brain damage, namely 0.1 to 0.3 Gm. After one-half hour blood samples were again obtained. When nitrous oxide was used specimens were obtained for control and then the gas was given in the concentration of 90 per cent to 10 per cent oxygen for one-half hour following which fresh blood samples were obtained and analyzed. In the specimens from the rabbits receiving nitrous oxide, the gas was corrected for by the method of Oreutt and Waters.<sup>6</sup>

### RESULTS

The results of these blood studies are shown in Tables II and III. It will be noted that the results show considerable variation in different animals and in the same animals at different times. Similar variation was noted by Eastman (Table IV) and is probably accounted for on the basis of factors previously mentioned; namely, uterine contractions, maternal activity, etc. The fetal blood specimens are obviously venous in origin and while the  $O_2$  content is somewhat lower the results are, in general, comparable to the readings obtained by Eastman and Smith in the human being. In neither mother nor fetus do our results reveal any significant alteration in blood  $O_2$  as a result of sodium pentobarbital or nitrous oxide administration.

TABLE IV. SHOWING THE OXYGEN RELATIONSHIPS OF MATERNAL AND FETAL BLOOD AT BIRTH EXPRESSED IN VOLUMES PER CENT

CASE	MATERNAL				FETAL			
	CAP.	CONT. ART.	CONT. VEN.	CAP. UNSAT.	CAP.	CONT. ART.	CONT. VEN.	CAP. UNSAT.
1	14.5	13.8	10.0	2.6	20.2	9.8	2.4	14.1
2	13.8	13.1	10.1	2.2	22.4	12.3	5.9	13.3
3	17.1	16.2	12.8	2.6	18.8	9.5	1.4	13.3
4	14.8	14.1	9.9	2.8	20.5	10.2	3.3	13.8
5	15.6	14.8	10.2	3.1	22.5	12.7	6.0	13.1
6	16.3	15.5	11.0	2.9	21.0	8.2	1.3	16.3
7	17.0	16.2	12.8	2.5	20.9	8.8	2.7	15.1
8	16.0	15.2	12.9	2.0	19.5	11.2	5.3	11.2
9	15.2	14.4	10.5	2.8	19.8	9.9	2.3	13.7
10	12.4	11.8	9.0	2.0	22.3	12.2	5.4	13.5
11	15.4	14.6	10.0	3.1	20.8	9.3	1.5	15.4
12	15.5	14.7	10.5	2.9	22.5	13.2	5.7	13.0
13	16.1	15.3	11.0	3.0	19.9	10.4	2.0	13.7
14	14.9	14.2	10.6	2.5	20.3	10.1	2.9	13.8
15	16.6	15.8	13.3	2.0	20.8	9.8	1.9	14.9
Average	15.4	14.7	11.0	2.6	20.8	10.5	3.3	13.9

TABLE III. PRENATAL ANESTHESIA WITH N<sub>2</sub>O 90% & O<sub>2</sub> 10% FOR ONE-HALF HOUR

NO.	DATE OF TERM	DAYS BEFORE TERM	MATERNAL										FETAL SAGITTAL SINUS BLOOD					
			OXYGEN				CARBON DIOXIDE						OXYGEN		CARBON DIOXIDE			
			ARTERIAL		VENOUS		ARTERIAL		VENOUS		BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER		
			BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER		
2	2/16	1	5.0*	7.4	1.5		47.1*	31.8	61.5*		0.2	0.5	54.9	45.3				
19	2/20	3			8.1	11.4			28.3	27.0								
23	2/28	4	8.3	9.9	10.8		41.9	33.5	35.8									
25	3/11	10	16.2	13.4	13.2	10.4	31.4	28.5	33.9	28.6								
8	3/28	10	12.4	12.2	12.9	12.2	44.4	44.0	49.0	43.4								
30	4/1	5	12.3	14.7	11.4	13.1	43.8	37.1	42.6	37.4								
9	4/6	1	5.7	8.1	12.6	2.7*	49.0	34.9	47.4	40.5*	0.6	1.0	62.7	46.9				
					14.4*				47.4*									
22	4/30	1		5.3	4.9*	2.4*		30.6	40.3*	32.6*	0.4	0.3	52.9	43.0				
36	4/21	5	3.3		3.0*	6.3*	30.8		33.7*	42.6*	0.2	0.4	44.7	45.5				
37	4/19	1	11.1	8.3*	0.7*	4.7*	34.9	38.6*	51.3	46.0*	0.1	0.0	54.5	61.4				
38	4/23	1	12.3	11.9	4.2	9.0	41.6	38.6	49.1*	35.7	0.2	0.9	61.4	45.8				
					15.2				40.6									
41	5/2	1	15.4	11.4	7.6*		35.4	28.5	38.3*		0.3	0.0	47.7	36.2				
23	5/5	1	11.9	8.8	11.6	7.6	26.7	24.3	29.1	29.2	0.2	0.4	60.5	35.1				
Average			10.4	10.1	8.8	8.9	38.8	33.7	41.9	36.3	0.3	0.4	54.9	44.9				
Standard deviation			4.0	2.8	4.8	3.8	7.04	5.4	8.8	6.8	0.15	0.34	6.03	2.44				

\*Blood taken from uterine vessel.

## DISCUSSION

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—Dr. Kretzschmar and his co-workers have carried out a very carefully planned experiment which is timely. As he mentioned, several men have attributed various degrees of fetal pathology to the use of barbiturates in the mother. Medicolegal complications have arisen in several localities. Dr. Kretzschmar has shown that in the rabbit many times the therapeutic dose of nembutal has no effect on the blood gases of the mother or fetus. Furthermore, they could demonstrate no damage to the brain.

Dr. Kretzschmar mentioned that animal experimentation cannot be compared with human beings. Barcroft has shown that the fetal hemoglobin of the rabbit, sheep, and goat takes up oxygen more readily than the human fetal hemoglobin does. He has also shown that there is a very exact regulation of the blood flow in the mother and fetus of these animals. The fetus lives in a very low percentage of oxygen but, so far as I know, no one has determined just how little oxygen the fetus actually needs. It is well protected and its movements are limited. These conditions probably account for the very low oxygen saturation in the fetal blood.

Another difference between the human being and the animal is in the type of placentation. Man and the higher apes are the only ones that have a hemochorial type of placenta, which permits easy and quick division of blood gases in both directions. I believe many of these studies on fetal respiration and the effect of drugs must be started on the human being. It is feasible during a cesarean section under local anesthesia to deliver the cord through a small incision in the uterus and obtain specimens of blood.

DR. FRED L. ADAIR, CHICAGO, ILL.—The oxygenation of the fetus does not depend upon the respiratory movements of the fetus but on its cardiac circulation. In other words, drugs might have an effect on the fetal respiratory apparatus which would not be quite comparable to what takes place in the newborn infant when the respiratory center is all important. One point I would like to have Dr. Kretzschmar discuss in his closing remarks is what effects, if any, were observed in the rabbits after they were delivered so far as the establishment of their respiration was concerned. I think this is particularly important, because the anoxemia which is quite prolonged sometimes does considerable harm to the newborn baby.

Another point is worthy of discussion: I understand that in these experiments the gases and anesthetics were given during pregnancy and not during labor. Of course, we give these agencies during labor in the human being, and it is not only the direct effect of these agencies on the fetus but on the course of labor and the uterine contraction that is important. I think we should understand that the uterine contractions have a very important function to perform in maintaining circulation in the uterine sinuses and, of course, anything that interferes with that will affect the fetus and alter its condition.

Dr. F. F. Snyder has been doing some very careful work on fetal respiratory movements in the rabbit. From his experiments it is quite obvious that the rabbit does have respiratory movements in utero, which, of course, have nothing to do with its oxygenation.

We do encounter definite changes in the fetus due to acute anoxemia. We see these changes resulting from the sudden death of the fetus, where there are petechial hemorrhages scattered throughout the viscera. The most classical example is where there is complete separation of the placenta which results in death of the fetus from acute anoxemia with numerous visceral petechial hemorrhages, and as a result there are changes in the brain. It is only reasonable to expect that there would not be such striking evidence of these changes, particularly in the brain, in the more slowly developing cases of anoxemia from analgesia. The knowledge that we do get them would lead us to anticipate changes in the brain cells which would not be discernible even under microscopic examination. This is an extremely complicated problem. It seems very difficult to get general agreement on such a fundamental fact as to whether or not the fetus has respiratory movements in utero. It is more difficult therefore to interpret some of these less concrete evidences of fetal respiration and circulation.

## DISCUSSION

The combined results of this study would seem to indicate that the likelihood of intrauterine cerebral anoxia with resulting cerebral damage in fetuses whose mothers are subjected to either sodium pentobarbital or nitrous oxide is remote. The fact that the pregnant animals were subjected to concentrations of both agents far in excess of the dose used clinically and yet gave birth to apparently normal fetuses whose brains showed no demonstrable injury points to the fact that no ill effects are suffered by the rabbit fetus in utero.

While we do not feel that these findings remove all criticism from the use of these agents, we are of the opinion that they tend to disprove the claims of Schreiber that they may be the frequent cause of serious cerebral damage to the fetus in utero. It is true that the results of this study in rabbits cannot be said to apply directly to the use of these agents in the human being, because of species differences, but it seems reasonable to assume that if they could cause damage certainly such intense doses would have produced some demonstrable evidence.

The fact that this study as well as others in the literature indicate that the fetal blood oxygen is normally much lower than that required for the adult, suggests that the fetal tissues are capable of using the available oxygen more efficiently or that the rapid rate of the fetal heart may result in an increased minute volume flow of blood which could satisfy the oxygen needs of the fetal tissues. This would account for the extremely low readings obtained in the specimens from the superior longitudinal sinus. It would also suggest that moderate variations in the maternal blood oxygen would be of less importance to the fetus than has been previously supposed. It would seem therefore that if any criticism of the use of these agents is justifiable it must be on some other basis than that they produce anoxia in utero with resultant cerebral damage.

This study suggests that since no significant changes were observed following such large doses of sodium pentobarbital and high concentrations of nitrous oxide that the clinical use of these agents in reasonable amounts would be unlikely to cause harm to the human fetus. Just what constitutes reasonable amounts of these drugs may be debatable, but it is our opinion that 0.1 to 0.3 Gm. of sodium pentobarbital may be safely used as an analgesic drug in obstetrics. While it has been demonstrated that nitrous oxide in the concentration of 90 per cent with 10 per cent oxygen can produce significant alterations of the blood gases in the adult, we feel that concentrations up to 75 per cent  $N_2O$  and 25 per cent  $O_2$  can be used without danger to either the mother or fetus.

We wish to express our appreciation to Miss Kathleen Sturgeon for her invaluable assistance in the administration of the anesthetics to the animals.

## REFERENCES

- (1) *Schreiber, Frederic*: J. Pediat. 16: 297, 1940. (2) *Eastman, N. J.*: Bull. Johns Hopkins Hosp. 47: 221, 1930. (3) *Steele, A. G., and Windle, W. F.*: J. Physiol. 94: 531, 1939. (4) *Smith, C. A.*: Surg., Gynec. & Obst. 69: 584, 1939. (5) *Van Slyke, D. D., and Neill, J. M.*: J. Biol. Chem. 61: 523, 1924. (6) *Orcutt, F. S., and Waters, R. M.*: J. Biol. Chem. 117: 509, 1937.



# A CONSIDERATION OF THE CAUSE AND POSSIBLE LATE EFFECT OF ANOXIA IN THE NEWBORN INFANT\*

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IT HAS been pointed out by Schreiber<sup>10, 11</sup> that serious neurologic manifestations in children are frequently associated with neonatal apnea. He postulates fixed degenerative brain lesions in the newborn as the result of "paranatal anoxia." If such a relationship exists, the responsibility of the obstetrician cannot be minimized.

The purpose of this study was first, to analyze the factors responsible for delayed respirations; and second, to determine the relationship between neonatal apnea and later mental development, providing methods were employed to administer oxygen during the apneic period. As anoxia may develop at any time during pregnancy and delivery, it is not possible to prevent all anoxic damage. Apnea, however, exists when the organism fails to breathe. In the absence of normal respirations, the newborn will become rapidly anoxic, unless oxygen is supplied. Oxygen may be supplied by administering oxygen to the mother as long as the cord pulsates. When pulsations cease, oxygen may be administered directly, if artificial respiration is maintained in the presence of oxygen.

## I. A CONSIDERATION OF THE VARIOUS OBSTETRIC FACTORS IN THE PRODUCTION OF DELAYED RESPIRATION IN THE NEWBORN INFANT

*Material and Methods.*—The records from 1,097 consecutive deliveries were studied. Ninety-two of these records were omitted. The omissions are tabulated in Table I. Seventy-three records had insufficient data. Babies weighing less than 1,000 Gm. were considered previsible. As only 5 cesarean sections were performed in this series, they were omitted. The purpose of the study required the omission of babies having no heart tones at the onset of labor. One hydrocephalic baby delivered following a craniotomy.

TABLE I. TABULATION OF OMITTED CASES

OMISSIONS	CASES	BABIES STILLBORN OR DIED
Insufficient data	73	2
Cesarean section	5	1
Previsible (under 1,000 Gm.)	6	6
Stillborn, no heart tones at onset of labor	7	7
Congenital anomaly (craniotomy)	1	1
Total	92	17
Total number of babies	1,097	

*Analgesia.*—Only one technique is used for all patients receiving analgesia. During the antenatal period an effort is made to prepare

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DR. FRANCIS C. GOLDSBOROUGH, BUFFALO, N. Y.—I do not think that we should carry the results of these experiments over to clinical practice, because in these experiments animals were given sedatives during pregnancy, the effect of which was entirely worn off when they were delivered. That is very different from giving sedatives to patients in whom the effect is still present when the child is delivered, so that it does not breathe properly and injuries to the child result.

DR. KRETZSCHMAR (closing).—I did not wish to create the impression that this study removes all of the criticism from the use of these analgesic and anesthetic agents. The study was undertaken to find out whether these drugs were capable of producing a sufficient decrease of oxygen level. If a depression of the fetus occurs sufficient to produce an apnea, then it is certainly conceivable that an anoxemia may develop. Conditions comparable to an acute anoxemia in the fetus in utero would probably be preceded by a serious condition in the maternal organism.

Some of the animals which were delivered at the time of section were perfectly normal and breathed readily. The administration of these substances did stop all evidence of intrauterine respiratory activity. I do not think we can eliminate the possibility that certain individuals are sensitive to or show toxic manifestations from these agents, but I do believe that the study tends to disprove that cerebral damage can be produced in utero by the administration of these agents to the mother during pregnancy or early in labor.

in the first few days of life are considered to be severely apneic. *Neonatal death* indicates an infant death occurring within twelve days of birth or before discharge from the hospital. These deaths are included as some may reflect the remote effect of cellular anoxia.

The incidence of apnea, stillbirth, and neonatal death for the cases omitted and for the cases to be analyzed is tabulated in Table II. The

TABLE II. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN CASES OMITTED AND IN ENTIRE SERIES

	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Entire series	1,097	82.3	8.7	5.8	1.8	1.4
Omitted	92	70.7	6.4	4.4	14.1	4.4
Series to be used	1,005	83.3	8.9	6.0	0.7	1.1

gross fetal mortality, 3.2 per cent for the entire series, is uncorrected and includes all previable babies. One and eight-tenths per cent of all babies were stillborn. The high incidence of stillbirths and neonatal deaths in the omitted group is explained by the fact that all previable babies and those with no heart tones at the onset of labor are included.

#### DATA

*Length of Labor.*—The incidence of neonatal apnea and fetal death in relation to the duration of labor is presented in Table III. It is fre-

TABLE III. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO DURATION OF LABOR

DURATION OF LABOR	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
0- 4 hours	31	80.6	6.5	12.9	0	0
5-11 hours	182	81.3	6.5	10.4	0.6	1.2
12-18 hours	80	85.0	7.5	6.3	0	1.2
18 plus hours	40	87.5	12.5	0	0	0
Average, all normal primiparas	333	82.9	7.5	8.4	0.3	0.9

quently stated that a long labor is detrimental to the baby. To eliminate conflicting factors only normal primiparous labors are considered. If during a long labor the mother receives ample rest, nourishment, and fluids and if operative procedures are avoided, long labor does not seem to be harmful to the baby. In the short and precipitate labors, there is a marked increase in the percentage of severely apneic babies.

*Duration of Second Stage.*—The incidence of neonatal apnea and fetal death in relation to the duration of the second stage and to outlet forceps deliveries, in otherwise normal primiparas, is shown in Table IV. Only normal primiparous deliveries have been considered, as multiparas cannot be said to have a true second stage. If abnormal labors had been included, the factor of unusual trauma would distort the figures. Very little difference is noted in the incidence of apnea, whether the second

each patient for labor. She is told to expect some pain but that "relief consistent with safety" to the baby will be given. As pains become hard, each patient receiving analgesia is given 3 gr. of pentobarbital sodium and  $\frac{1}{200}$  of a gr. of scopolamine. After forty-five minutes,  $\frac{1}{400}$  of a gr. of scopolamine is given, and the latter is repeated as often as necessary thereafter but not more often than every two hours. This dosage is smaller than that frequently employed, and, of course, the percentage of satisfactory amnesia is also lower. No attempt has been made to obtain complete amnesia. Extreme restlessness is unusual following this regime.

With bulging in primiparas or complete dilatation in multiparas, 50 per cent nitrous oxide and oxygen is given with each pain, and expulsive efforts are encouraged. In all primiparas and in multiparas with strong perineal bodies, local infiltration anesthesia is employed as crowning occurs. At the proper time a *deep* episiotomy permits the head to deliver with very little resistance. When necessary, low or midforceps may be applied and traction used during the pains with no general anesthesia. Following this regime, anesthesia is a minimal factor in the production of "paranatal anoxia." Neither pituitrin nor ergonovine is given to hasten separation of the placenta.

*Oxygen.*—Immediately following the birth of the head, the 50 per cent nitrous oxide-oxygen mixture is discontinued and oxygen is given. The mother breathes oxygen until the cord stops pulsating. In many cases only oxygen is given because nitrous oxide is omitted if the analgesia is satisfactory.

*Newborn Care.*—The baby is placed on the mother's abdomen immediately following birth, covered to preserve warmth and left undisturbed until pulsations in the cord cease. Mucus is removed by means of a soft rubber ear syringe. The time interval between birth, the first regular breathing, and the first vigorous cry is recorded in all cases. We have classified the respiratory response as, *no apnea*, *mild apnea*, *severe apnea*, and *stillborn*. *No apnea* is said to exist, if at birth the color is good or improves quickly and if the baby breathes regularly in less than thirty seconds. The baby is not considered apneic if breathing is regular and the color good, even though the cry is delayed. *Mild apnea* indicates a slightly delayed response, respirations being delayed more than thirty seconds but well established in one minute or less. In this type cyanosis clears promptly as breathing becomes regular. *Severe apnea* is said to be present if both breathing and crying are delayed more than one minute. An attempt is made to supply oxygen to these babies through the cord until pulsations cease or until signs of placental separation are present. Then if spontaneous respirations have not occurred, gentle artificial respiration in the presence of oxygen or oxygen and  $\text{CO}_2$  is started. As every effort is made to prevent anoxia in all apneic babies, we do not wait for long intervals to see if resuscitation is necessary. Once respirations are established, oxygen and  $\text{CO}_2$ , if employed, is discontinued and oxygen is given until the color remains pink. During resuscitation the baby is kept warm either in a crib or in a warm bath and the air passages are kept clear. All babies developing cyanosis

TABLE VI. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO NORMAL AND ABNORMAL DELIVERIES

TYPE OF DELIVERY	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
All normal cases	815	87.5	6.9	4.8	0.2	0.6
All abnormal cases	190	65.8	17.4	11.0	2.1	3.7
Average all cases	1,005	83.3	8.9	6.0	0.7	1.1

All abnormal deliveries are included in one group, since the trauma in abnormal deliveries is of the same type, varying only in degree. Whether delivery is accomplished by the use of outlet or midforceps, or by version or breech extraction, the head is delivered through the pelvis with more sudden compression than is found in normal deliveries. There is a marked increase in mild apnea, severe apnea, stillbirths, and neonatal deaths following abnormal deliveries, with a possibility of serious anoxia prior to delivery.

*Parity.*—The incidence of neonatal apnea and fetal death in relation to parity is shown in Table VII. When analgesia is not used the per-

TABLE VII. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO PARITY

PARITY	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Normal multiparas	264	91.2	5.7	1.9	0.4	0.8
(no analgesia)						
Normal primiparas	65	89.3	7.7	1.5	0	1.5
(no analgesia)						
All multiparas	554	86.6	8.3	3.1	0.7	1.3
All primiparas	451	79.4	9.5	9.5	0.7	0.9

centage of nonapneic babies is about the same in primiparas as in multiparas. However, when all multiparas are compared with all primiparas, there is a marked decrease in the percentage of nonapneic babies in the primiparous group. An important contributing factor, to the increased percentage of apneic babies in the "all primiparous group," is the inclusion of those babies delivered by outlet forceps.

*Maternal Anemia.*—The incidence of neonatal apnea and fetal death in relation to maternal anemia is shown in Table VIII. As parity did

TABLE VIII. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO MATERNAL ANEMIA

MATERNAL HEMOGLOBIN	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Under 11.0 Gm.	20	75.0	10.0	10.0	5.0	0
11-12.9 Gm.	232	86.2	9.9	3.0	0	0.9
13-14.9 Gm.	465	88.0	5.4	6.0	0.4	0.2
15 Gm. and over	98	90.9	6.1	2.0	0	1.0
Average all normal primiparas and multiparas	815	87.5	6.9	4.8	0.2	0.6

TABLE IV. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO DURATION OF SECOND STAGE AND TO OUTLET FORCEPS DELIVERIES IN OTHERWISE NORMAL PRIMIPARAS

DURATION OF SECOND STAGE	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
0-1 hour	212	84.4	5.2	9.4	0.5	0.5
1-2 hours	82	81.7	11.0	7.3	0	0
Over 2 hours	39	77.0	12.8	5.1	0	5.1
Average, normal primiparas	333	82.9	7.5	8.4	0.3	0.9
Outlet forceps	76	75.0	13.2	10.5	0	1.3

stage lasts one or two hours or if it is less than one hour in duration. When the second stage lasts longer than two hours, there is definite evidence of fetal injury.

The figures for simple outlet forceps have been included, as this type of delivery is frequently chosen in the belief that the procedure prevents trauma to the baby's head. The incidence of apnea is high when outlet forceps have been used. Cole and associates<sup>1</sup> noted, "Asphyxia occurs with considerably greater frequency in low forceps delivery than in spontaneous delivery. However, in most of these cases episiotomy is also performed, which necessitates anesthesia." In our group no general anesthesia was given, as local anesthesia makes the use of outlet forceps almost painless after a *deep* episiotomy is performed. The incidence of apnea is higher when outlet forceps are used than when the second stage is two hours or less in duration. The evidence indicates that unless the second stage is unduly prolonged, the practice of purely conservative obstetrics produces fewer apneic babies.

*Rupture of Membranes.*—The incidence of neonatal apnea and fetal death in relation to the time of rupture of membranes is shown in Table V. Only normal primiparous deliveries are included in this group. Ab-

TABLE V. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO TIME OF RUPTURE OF MEMBRANES

MEMBRANES RUPTURED	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Early	94	73.4	8.5	16.0	0	2.1
Late	221	86.3	6.8	5.9	0.5	0.5
Not noted	18	88.8	11.2	0	0	0
Average, all normal primiparas	333	82.9	7.5	8.4	0.3	0.9

normal deliveries are omitted as the resultant trauma would influence the percentage of apneic babies. Normal multiparas are omitted as their inclusion would minimize the importance of trauma incident to the dilatation of a nulliparous birth canal. It would seem that the membranes serve a protective purpose as there is a marked increase in mild and severe apnea and neonatal death when the membranes are ruptured early in labor. The membranes are said to have been ruptured early if the rupture occurred prior to the onset of labor or early in the first stage.

*Abnormal Deliveries.*—The incidence of neonatal apnea and fetal death in relation to normal and abnormal deliveries is shown in Table VI. Trauma plays an important role in the production of apneic babies.

TABLE XI. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO DEGREE OF ANALGESIA

DEGREE OF ANALGESIA	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Good amnesia	151	81.3	11.4	6.0	0	1.3
Excitement, good amnesia	21	81.0	4.8	9.4	4.8	0
Poor amnesia	96	81.3	2.1	16.6	0	0
Average all normal primiparas with analgesia	268	81.3	7.5	10.1	0.7	0.4

Table XII. The highest percentage of apneic babies is noted if the time interval is from one to two hours. If the time interval is more than two hours the incidence of apnea decreases.

*Prematurity.*—The incidence of neonatal apnea and fetal death in relation to prematurity is shown in Table XIII. Our results are similar to those published by others, indicating a great increase in severe apnea and fetal death in prematures when compared with the mature group. As maturity advances, the effects of trauma are less severe, even when abnormal deliveries are considered.

TABLE XII. INCIDENCE OF NEONATAL APNEA IN RELATION TO TIME OF ADMINISTRATION OF ANALGESIC DRUG

INTERVAL BETWEEN ADMINISTRATION OF ANALGESIC DRUG AND DELIVERY	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
One hour or less	167	85.0	7.8	6.6	0	0.6
One to two hours	194	83.5	7.2	8.3	0.5	0.5
Two to three hours	66	87.8	7.6	4.6	0	0
Over three hours	59	88.1	6.8	5.1	0	0
Average all normal primiparas and multiparas	486	85.2	7.4	6.8	0.2	0.4

TABLE XIII. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO PREMATUREITY

WEIGHT OF BABY	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
1,000 to 2,500 Gm.	25	72.0	4.0	16.0	0	8.0
2,500 to 4,000 Gm.	718	88.0	6.7	4.6	0.3	0.4
Over 4,000 Gm.	72	87.5	9.7	2.8	0	0
Average all normal primiparas and multiparas	815	87.5	6.9	4.8	0.2	0.6

## II. A PRELIMINARY REPORT ON THE RELATIONSHIP BETWEEN DELAYED RESPIRATION AT BIRTH AND LATER MENTAL AND PHYSICAL DEVELOPMENT

The purpose of this portion of the study was to determine the value of supplying oxygen to all babies during the apneic period. As the number of apneic babies in this group is too small to be of statistical significance this discussion is in the nature of a preliminary report. It is

not greatly alter the incidence of apnea in normal deliveries, both multiparas and primiparas are included in this analysis. Except in cases of post-partum hemorrhage, the hemoglobin reading was taken on the fourth post-partum day. It will be noted that each group presenting a better average hemoglobin had a lower incidence of apnea. The same trend is shown when this group is separated into those having analgesia and those without analgesia. However, in the patients having a severe degree of anemia, if analgesia is given, the incidence of severe apnea is increased.

*Analgesia.*—The incidence of neonatal apnea and fetal death in relation to analgesia is shown in Table IX. A definite increase in severe

TABLE IX. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO ANALGESIA

	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
All analgesia	486	85.2	7.4	6.8	0.2	0.4
No analgesia	329	90.9	6.1	1.8	0.3	0.9
Average all normal primiparas and multiparas	815	87.5	6.9	4.8	0.2	0.6

apnea is noted in the analgesia group. The higher infant mortality in the "no analgesia group" can be explained by the fact that analgesia was withheld in patients having ante-partum hemorrhage or showing signs of toxemia when fetal heart tones were present.

The relation of parity and normal and abnormal delivery to the degree of analgesia is shown in Table X. Less than 50 per cent had

TABLE X. THE RELATION OF PARITY, NORMAL AND ABNORMAL DELIVERY TO DEGREE OF ANALGESIA

TYPE OF DELIVERY	CASES	DEGREE OF ANALGESIA		
		GOOD AMNESIA	AMNESIA BUT EXCITEMENT	POOR AMNESIA
Normal multiparas	218	13.7	8.3	78.0
Abnormal multiparas	32	15.6	18.7	65.7
Normal primiparas	268	42.2	20.9	36.9
Abnormal primiparas	109	67.0	5.5	27.5
Average all cases	627	41.4	8.1	50.5

satisfactory amnesia. This very low figure is undoubtedly due to the small amount of analgesic drug used. Eight and one-tenth per cent of all patients receiving analgesia exhibited some degree of excitement.

The incidence of neonatal apnea and fetal death in relation to the degree of analgesia is shown in Table XI. Only normal primiparous labors are considered, as other factors alter the relationship if the entire group is analyzed. If birth occurs during the excitement stage there is an increase in the percentage of fetal deaths. The high incidence of severe apnea in those receiving poor amnesia may be due to an unusual reaction to the drug used.

The incidence of neonatal apnea in relation to the time interval between birth and the administration of the analgesic drug is shown in



undesirable deviations from a normal development, and low scores represent a desirable deviation from the typical behavior of a group of children.

#### DATA

The distribution of intelligence quotients in the entire group of 270 children is shown in the histogram in Fig. 1. The median is 112.4, the average 111.4. In Fig. 2 the distribution of I. Q.'s of 159 children is shown. No analgesia was used in this series. The median I. Q. was 111.7 and the average I. Q. was 110.8. In Fig. 3 the distribution of I. Q.'s of 111 children is shown. Analgesia was used in this group. The median I. Q. was 113.2 and the average I. Q. was 112.3. In Fig. 4 the distribution of I. Q.'s for 34 children who were asphyxiated at birth is shown. The median I. Q. was 110.4, and the average I. Q. was 112.1.

The median scores on the Haggerty-Olson-Wickman rating schedules as well as normative values reported by Haggerty-Olson-Wickman<sup>4</sup> are shown in Table XVI. Separate medians are not reported according to

TABLE XVI. MEDIAN SCORES ON THE HAGGERTY-OLSON-WICKMAN BEHAVIOR RATING SCHEDULES "A" AND "B"

	CASES	MEDIAN SCORE	
		SCHEDULE "A"	SCHEDULE "B"
"No analgesia" group	159	8.9	64.5
"Analgesia" group	111	9.7	63.0
"Asphyxia" group	34	7.0	62.9
Normative value*		8.6	65.4

\*From Haggerty, Olson and Wickman.<sup>4</sup>

sex, as the number of cases is, as yet, too small. This series fails to reveal a marked trend, as there is no striking difference between the various groups of cases. The data tend to indicate that behavior problems occur with no greater frequency in our children who were asphyxiated at birth than in average children tested by Haggerty, Olson, and Wickman.<sup>4</sup>

#### DISCUSSION

Serious anoxia occurring during pregnancy and labor may be responsible for many stillbirths and neonatal deaths. In addition, a relationship between birth injury and later degenerative lesions in the brain has been reported by many neurologists. Schreiber<sup>11</sup> noted that 70 per cent of a large group of children, having brain defects, were found to have been asphyxiated at birth. Various mechanisms may operate to deprive the fetal brain tissue of oxygen. Barcroft<sup>3</sup> and Peters and Van Slyke<sup>9</sup> have classified anoxia as anoxic, anemic, stagnant, and histotoxic. In anoxic anoxia the arterial blood is insufficiently saturated with oxygen. Anemic anoxia results when the oxygen-carrying power of the blood is decreased. Stagnant anoxia occurs if less than the normal amount of circulating blood is carried to the cells. Histotoxic anoxia will develop even though the oxygen supply is normal if the cells are so altered that they cannot utilize the available oxygen.

During pregnancy one or more of these mechanisms may operate to produce anoxia. Premature separation of the placenta, placental disease, nitrous oxide anesthesia given for minor operations, pneumonia

our intention to continue testing the local children each year, as they are admitted to the public school system, until the series is large enough to be of clinical importance.

*Material and Methods.*—Eight hundred and sixty-one consecutive births were used in this follow-up study. Owing to peculiar local conditions a large number of patients come from distant points. Therefore it was possible to make tests on only 270 children. Of the 861 babies, 29 failed to survive. As all previables were included, the uncorrected fetal mortality was 3.3 per cent. Eight hundred and thirty-two babies were discharged from the hospital alive. The present status of the 832 is shown in Table XIV. A summary of the birth records of the 270 children, now in school, is shown in Table XV.

TABLE XIV. TABULATION OF OMITTED CASES

Children in school and tested	270
Children out of school—not tested (injury, rheumatic fever, etc.)*	9
Died after discharge from the hospital†	8
Nonresidents	378
Moved	155
Unable to trace (moved?)	3
Illegitimate (not known)	9
Total	832

\*It is planned to test these children as the study is completed.

†Five died of upper respiratory infections; two were cretins; one died of accidental causes; only one, a premature cretin, was apneic at birth.

TABLE XV. INCIDENCE OF NEONATAL APNEA ON TESTED CHILDREN

	CASES	PER CENT		
		NO APNEA	MILD APNEA	SEVERE APNEA
No analgesia	159	96.2	2.5	1.3
Analgesia	111	74.8	17.1	8.1
Total	270	87.4	8.5	4.1

Two methods of testing the 270 school children were used. First, each child was given the *Kuhlmann-Anderson*<sup>7</sup> *Intelligence Tests*. These tests were conducted by examiners working under well-trained supervision. The tests were scored by one individual. From this data median and average intelligence quotients were obtained for the entire group, for those having analgesia, for those in whom analgesia was not employed, and for the group that were apneic at birth.

To supplement the *Kuhlmann-Anderson*<sup>7</sup> tests, the Haggerty-Olson-Wickman<sup>4</sup> behavior rating schedules were used. This evaluation demonstrates both the weaknesses and assets of the individual child. One portion of the tests tends to bring out the frequency of various behavior problems. The balance of the test gives a graphic rating for various intellectual, physical, social, and emotional traits. The schedules were completed in each case by the teacher who was in daily contact with the child. Schedule A in the test consists of a list of behavior problems occurring in elementary school children, and Schedule B consists of a graphic scale for each of the 35 intellectual, physical, social, and emotional traits that go to make up a well-developed child. In each schedule a high score depicts too frequent occurrence of behavior problems or

with inadequate aeration or the use of sulfanilamide and other drugs which reduce the oxygen carrying power of the blood may contribute to intrauterine anoxia. Eclampsia with its resultant physicochemical alteration of the cell may interfere with cellular oxidation.

Anemia may be an important factor in producing anoxia at any time during pregnancy or labor. An increase in severe apnea is noted when the maternal hemoglobin is below 11.0 Gm. Our study was made at an altitude of approximately 3,300 feet. It is possible that in lower altitudes a lower level of hemoglobin would be necessary to demonstrate such a high incidence of severe apnea. As a physiologic anemia is frequent during pregnancy, and as inadequate diet, poor living conditions, cardiac disease, or acute infections may be superimposed, a severe anemia may develop. In addition, threatened abortion with hemorrhage or hemorrhage from placenta previa or premature separation of the placenta may rapidly produce severe anemia with resultant anemic anoxia. All anemias of pregnancy should be treated and any patient whose hemoglobin is below 11.0 Gm. should be given blood if the response to medication is slow.

During labor if fever is present, the unusual demand for oxygen may limit the supply to the fetus. Pressure on the cord, a knot in the cord, or tight coils about the neck may also serve to prevent an adequate amount of oxygen reaching the fetus. Any trauma or increased pressure on the baby's head prevents free circulation, and as a result the blood carries less oxygen to the brain and may produce stagnant anoxia with resultant degenerative changes in the cerebral cells. This is perhaps the most frequent cause of neonatal anoxia, as in every labor the baby's head is subjected to trauma during both the first and second stages. If unusual trauma is present, and intracranial pressure increases due to cerebral edema or hemorrhage, localized areas may be deprived of oxygen with resultant necrosis. Hartman<sup>5</sup> has shown that trauma without demonstrable fracture, produces cerebral lesions similar to those produced by other anoxic factors. The normal expellant powers of labor produce a mild concussion. If these powers are abnormally great or if disproportion exists, an increase in the incidence of anoxia would be expected.

Histotoxic anoxia may occur during labor or delivery if dehydration is permitted to develop. Dehydration produces a relative concentration of cellular elements, and as a result the cell does not utilize all the available oxygen. During long or complicated labors every precaution must be taken to avoid dehydration, starvation and fatigue. All of the common drugs used to relieve pain during labor have been shown to increase the incidence of neonatal apnea. Cole and associates<sup>1</sup> have shown that even the use of acknowledged pharmacologic doses of scopolamine, morphine, or the common barbiturates greatly increase the degree of neonatal apnea. This dosage is much less than that generally used for full analgesia in obstetrics. The incidence of apnea was increased in our series even though small amounts of pentobarbital sodium and scopolamine were given. A high incidence of severe apnea was noted in the babies born of mothers who became excited. Regardless of cause,

NO. OF CASES

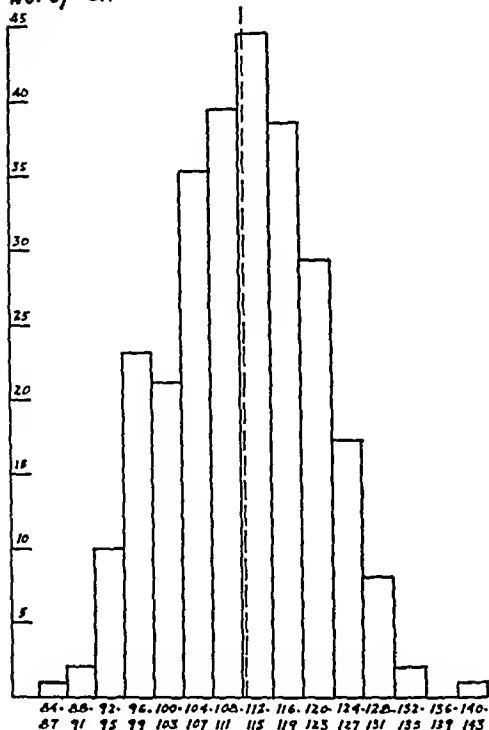


Fig. 1.

NO OF CASES

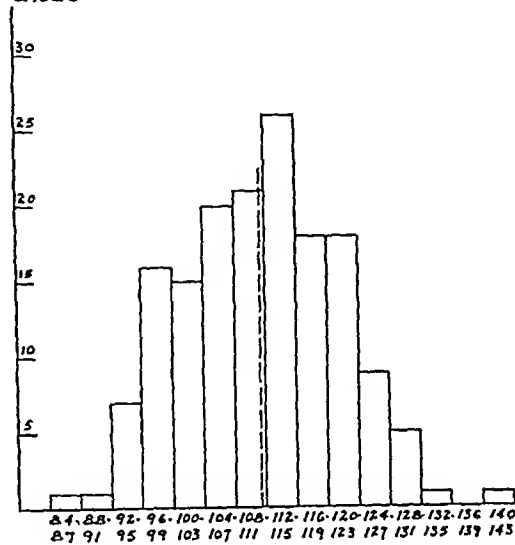


Fig. 2.

Fig. 1.—Histogram showing distribution of I. Q. for entire group tested (270 cases); median 112.4 (dotted line), average 111.4.

Fig. 2.—Histogram showing distribution of I. Q. for "no analgesia group" (159 cases); median 111.7 (dotted line), average 110.8.

NO. OF CASES

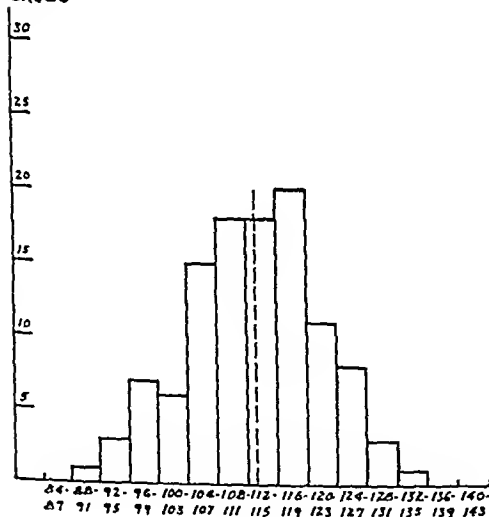


Fig. 3.

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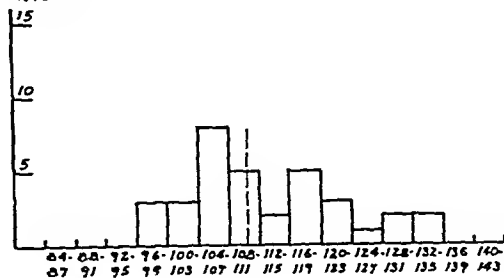


Fig. 4.

Fig. 3.—Histogram showing distribution of I. Q. for "analgesia group" (111 cases); median 113.2 (dotted line), average 112.3.

Fig. 4.—Histogram showing distribution of I. Q. for "asphyxiated group" (34 cases); median 110.4 (dotted line), average 112.1.

Fig. 5, a composite of the tabulated data, demonstrates the influence of various factors in the production of neonatal apnea. The white portion of the bar indicates the percentage of babies crying immediately after birth. The most important factor, trauma, may be produced by abnormal delivery, premature rupture of the membranes, outlet forceps, long second stage, or rapid labor. In premature babies, even a normal delivery may be associated with considerable trauma. Some of the factors producing apnea cannot be avoided but cumulative factors in these patients should be prevented. Maternal anemia should be controlled either by the routine use of some iron preparation or by the use of iron if indicated. Analgesia should be avoided if some uncontrollable factor such as anemia or prematurity is present. If analgesic medication is used an elective operative delivery should be postponed until the effect of the drug used is minimal. Eastman<sup>2</sup> and Henderson<sup>6</sup> have emphasized that the brain tissue of an infant is most susceptible to oxygen want. Yant,<sup>13</sup> Schreiber and Gates,<sup>12</sup> Hartman,<sup>5</sup> and others have shown that lesions in the brain are identical in all deaths from anoxia, regardless of cause. Schreiber<sup>11</sup> believes that even though the symptoms of cerebral anoxia may be alarming, complete recovery of function is possible, providing an adequate supply of air or oxygen is available before prolonged deprivation results in irreversible cellular destruction.

Neonatal apnea cannot be prevented entirely. Eastman<sup>2</sup> has said: "We hold to the belief that asphyxia neonatorum, in all of its manifestations, is an example of profound oxygen want. For this reason the one urgent necessity in its treatment is oxygen, and by the same token, the one urgent requirement in its prevention is oxygen." We have attempted to prevent anoxia by giving oxygen freely during the latter part of the second stage of labor. Every mother is given oxygen as long as the cord pulsates, and if the baby is apneic, oxygen or oxygen and CO<sub>2</sub> are supplied by means of gentle artificial respiration when pulsations in the cord cease. In addition, an attempt is made to reduce the incidence of neonatal apnea by the prevention of anemia and dehydration; by restricting operative procedures to absolute indications; by avoiding early rupture of the membranes if possible; by using only small amounts of analgesic drugs; and by supplementing light anesthesia with local anesthesia.

Intelligence and behavior tests were made on 270 school children in order to evaluate this procedure. Adequate birth records were available for all of these children. The number studied is, as yet, too small to be of statistical significance. The median of the entire group is high when compared with tests on general population groups, which may be partially accounted for by the economic group included in the study. Thirty-four, who had been apneic at birth, had a median I. Q. of 110.4 as compared with a median of 100 in general studies. Of the apneic group, only 3 were below 100. The lowest I. Q. was 97. Five of the 34 had an I. Q. above 125. It is said that an I. Q. above 125 indicates superior intelligence. Even though only a small series has been studied,

excitement is one of the first signs of cerebral anoxia. A baby born of a mother showing signs of anoxia would be very likely to be apneic at birth. The question of whether to use analgesic drugs and how much should be used, must be weighed carefully against the possible increased incidence of neonatal apnea and possible destructive cerebral anoxia. If the mother is properly prepared, most labors can be conducted with fair pain relief even though small amounts of analgesic drugs are used. In our series 50 per cent of the patients received satisfactory pain relief. If small doses are used, the undesirable effects of histotoxic anoxia can be reduced.

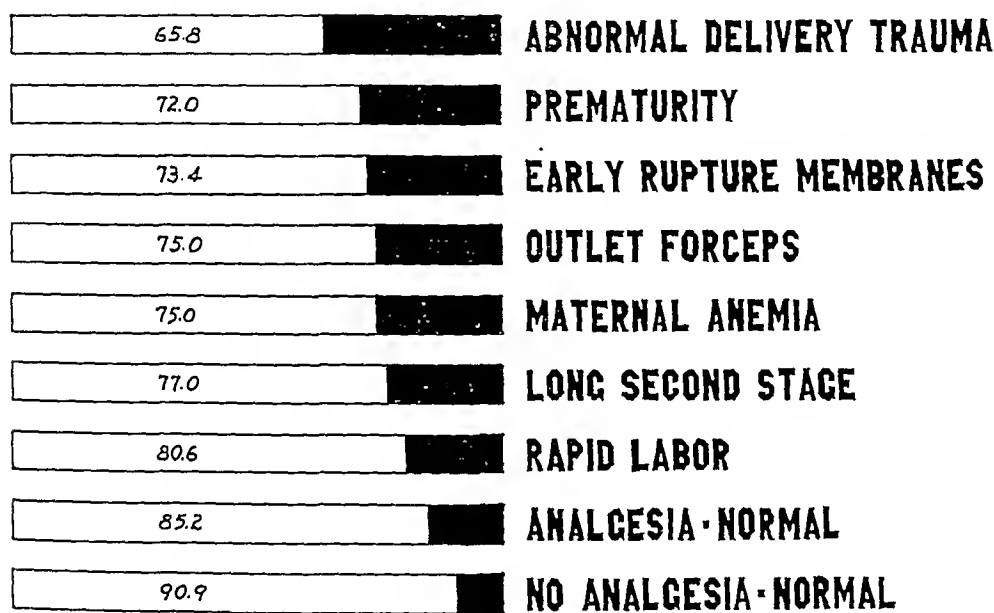


Fig. 5.—The effect of various obstetric factors in the production of neonatal apnea.

During delivery the use of nitrous oxide-oxygen as an anesthetic agent may produce oxygen want. Murphy<sup>8</sup> states that surgical anesthesia, defined as a state of muscular relaxation with adequate oxygen concentration, cannot be produced by nitrous oxide and oxygen. Eastman<sup>2</sup> has shown that nitrous oxide-oxygen anesthesia given for periods of less than five minutes, and in proportions of 85:15 or weaker, does not cause a harmful degree of anoxia. In the cases presented in this study, 50 per cent nitrous oxide and oxygen, supplemented by local anesthesia, was employed. This method permits the use of nitrous oxide as a relatively weak analgesic agent. If the danger of a harmful degree of anoxia is avoided, the objections to the nitrous oxide-oxygen mixture disappear.

After delivery, anoxic anoxia may occur if the air passages are not clear. Prompt removal of mucus in all babies immediately after birth seems to stimulate respiration, as it is rarely necessary to use a tracheal catheter. Neonatal anoxia may not develop for some hours or days after birth. This type may be due to increased intracranial pressure, a result of cerebral edema or hemorrhage.

allows us to reduce the scopolamine by half and get the same amount of amnesia. Some of the men are still using small doses of morphine, but most of us have eliminated morphine entirely.

It is my experience that the analgesia is not necessarily the cause of the asphyxia. It is more likely to be due to the general anesthetic which is given at the time of delivery. We have used chloroform for a long time, and I believe from the work of Eastman that chloroform has less asphyxiating effect than any other anesthetic. The trick is to give chloroform openly and slowly. With the combination of scopolamine, the barbiturate and this general anesthetic we see very little asphyxia. Nitrous oxide given at the time of delivery has shown a very definite increase in asphyxia.

So far as the question of the intelligence quotient of these children is concerned, I think what Dr. McPhail has brought out is just about what one would expect. When we started using twilight sleep we were criticized because of the aftereffects on the child, but on account of its transitory character, I always felt there would be no permanent effect either on the mother or the child.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—In New York we have become interested lately, through a report from the Health Department, in the enormous problem of the crippled child in the educational system. A study was made of these crippled children over a period of three to five years and an attempt was made to develop some knowledge as to the causation of these conditions. The obstetric influence in this investigation was not a very important or definite one, because the entire subject was dismissed with the statement that in one-third of all these cases birth trauma was given as the cause of the crippling.

A few of us rather demurred at that wholesale designation, and we have appointed in the Academy of Medicine a Committee to study this entire subject of congenitally crippled children through the medium of a group that includes the obstetrician, neurologist, pediatricist, and orthopedist. It was found that in this survey about three-tenths of those under investigation had developed cerebral palsy. Now it is easy enough to ascribe the development of cerebral palsy to obstetric injury if the mother is simply asked whether she had a forceps delivery. Of course, nowadays a large proportion of women are delivered by instrumental means, and it is hardly fair to attribute the occurrence of cerebral palsy to the trauma at birth simply by asking that one question.

What Dr. McPhail has said about the aftereffects on the future intellectual life of the child is very important, and I think we must solve the problem of the occurrence of such crippling conditions by a much wider investigation. Several of the men who came into these conferences admitted quite freely, men who had large experience with cerebral palsy, that trauma did not enter into the problem at all.

Unfortunately, these children do not die at an early age, and there is little possibility of getting autopsies, but the men who have observed these children came to the conclusion that in many of the cases we were not dealing with any injuries that could be attributed to the labor but rather with some shortcomings in the development of their nervous systems. So, while Dr. McPhail's observations are of great interest, I do not believe they will help us a great deal in any attempt to find the underlying causes in such unfortunate conditions as cerebral palsy and similar disturbances. However, I think we should be very grateful if a definite study along the lines he has pursued could be more universally developed throughout the country so that we might get some definite knowledge as to the underlying conditions that develop in these children later in life.

DR. WILLIAM E. CALDWELL, NEW YORK, N. Y.—Dr. McPhail has pointed out that a long, slow labor does not necessarily mean an apneic baby. It is the strong spasmodic contractions of the uterus against the resistance of the soft parts or the bony pelvis that gives apneic babies and birth injuries, especially in premature babies.

Asphyxia per se should increase the fetal heart rate. The slowing fetal heart means that there is obstruction to the fetal circulation necessitating the slowing heart to overcome such an obstruction. With the rupture of the membranes and with the descent of the head into the pelvis, the placental site is greatly com-

it would seem safe to say that the figures do not indicate mental retardation in the apneic group. If such a conclusion is permissible, this preliminary study indicates that apnea may be present at birth without severe anoxia and its resultant cerebral damage, providing oxygen is administered during the apneic period.

### CONCLUSIONS

1. Abnormal delivery, prematurity, early rupture of the membranes, outlet forceps, maternal anemia, long second stage, rapid labor, and the use of analgesic drugs are important factors in the production of neonatal apnea.

2. The incidence of neonatal apnea may be reduced by the prevention of anemia and dehydration; by restricting operative procedures to absolute indications; by preserving the membranes if possible; by using small amounts of analgesic drugs; by supplementing light anesthesia with local anesthesia; and by the liberal use of oxygen.

3. The importance of recognizing the factors frequently associated with neonatal apnea is stressed so that we may avoid, if possible, superimposing factors which would tend to increase the incidence of serious cerebral anoxia.

4. Two hundred and seventy school children were studied, using standard intelligence and behavior tests. At birth each of these children had received oxygen until respirations were established and until the color remained pink. The data tend to show that the few babies who were apneic at birth, did not show evidence of mental retardation when they reached school age.

### REFERENCES

- (1) Cole, W. C. C., Kimball, David C., and Daniels, L. E.: J. A. M. A. 113: 2038, 1931.
- (2) Eastman, Nicholson J.: AM. J. OBST. & GYN. 31: 563, 1936.
- (3) Barcroft, Joseph: The Architecture of Physiological Function, New York, 1934, The Macmillan Company.
- (4) Haggerty, M. E., Olson, W. C., and Wickman, E. K.: Haggerty-Olson-Wickman Behavior Rating Schedules, New York, 1930, World Book Company.
- (5) Hartman, F. W.: Am. J. Clin. Path. 8: 629, 1938.
- (6) Henderson, Yandell: Adventures in Respiration, Baltimore, 1938, The Williams and Wilkins Company.
- (7) Kuhlmann, F., and Anderson, Rose G.: Kuhlmann-Anderson Intelligence Tests for Ages Six to Maturity, ed. 5, Educational Test Bureau, Minneapolis, 1940.
- (8) Murphy, Frank J.: Surg., Gynec. & Obst. 70: 741, 1940.
- (9) Peters, John P., and Van Slyke, Donald D.: Quantitative Clinical Chemistry, Vol. I, Baltimore, 1931, The Williams and Wilkins Co.
- (10) Schreiber, Frederic: J. A. M. A. 111: 1263, 1938.
- (11) Idem: J. Pediat. 16: 297, 1940.
- (12) Schreiber, Frederic, and Gates, Nathaniel: J. Michigan M. Soc. 37: 145, 1938.
- (13) Yant, W. P., Chornyak, John, Schrenk, H. H., Patty, F. A., and Sayers, R. R.: Studies in Asphyxia, Public Health Bulletin, No. 211, Washington, 1934.

### DISCUSSION

DR. OTTO H. SCHWARZ, St. Louis, Mo.—Dr. McPhail shows very conclusively that there is increase in the asphyxia during analgesia. He also states that he does not carry this analgesia out to the extent where amnesia is to be expected, although a certain percentage of his patients have complete amnesia.

In St. Louis for a number of years, we gave analgesia excessively. We started in 1915 and used the original method of Gwathmey and continued using that method until about eight or nine years ago when we substituted barbituric acid by mouth. Recently we have been using seconal,  $1\frac{1}{2}$  to 3 gr., with scopolamine. The seconal



# VITAMIN THERAPY IN VULVAR DERMATOSES\*

## COMPONENTS OF THE B COMPLEX

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THE clinical similarity of mycotic vulvitis to chronic atrophic vulvitis was emphasized in 1937, but the underlying cause for the latter condition was not explained. While pursuing this problem, it became necessary to investigate the influence of at least some of the vitamins, especially factors of the B complex. To 15 cases of chronic atrophic dermatitis of the vulva, 5 cases of an undetermined type of vulvitis and 2 cases of unexplained vulvar pruritus are added to make a total of 22 individuals studied with respect to clinical and symptomatic responses to single and combined factors of the vitamin B complex.

Although unexpected improvements occurred in some, others did not yield to the same therapy. By election this evaluation is concerned with the importance of thiamin hydrochloride ( $B_1$ ), alone or with riboflavin ( $B_2$  formerly G), nicotinic acid or nicotinamide, pyridoxine ( $B_6$ ), and calcium pantothenate. The procedure followed on the whole the trial and error method, because so far the enormous literature lacks reference to a concrete program for such an investigation. The dosage needs establishment. Considerable ignorance exists regarding the interrelationship not only of these five members of the vitamin B complex but also of the other B factors as well as vitamins A, C, D, E, and K.

As proposed by Adair and Davis, the term chronic atrophic dermatitis of the vulva is employed at the Chicago Lying-in Hospital to designate chronic atrophic vulvitis, leucoplakic vulvitis, kraurosis in the broad sense, and other such synonyms.

## LITERATURE

Microscopic examination makes positive the diagnosis, yet the lucid and photographic descriptions by Taussig, Adair and Davis, and Hunt and Bonney and others offer support to the clinical or macroscopic diagnosis of chronic atrophic dermatitis of the vulva. From two to four stages are recognized by most investigators. Adair and Davis and Taussig agree upon three stages. The importance of differential diagnosis stands out when one notes the unanimity of opinion in the literature. Taussig earlier and then Hunt recorded in detail pathologic and symptomatologic aspects of chronic atrophic vulvitis.

Some differences prevail on the therapeutic approach. Montgomery and Counseller recommend nerve resection, a few counter with nerve blocking much after the pattern of Wilson by alcoholic injection. The majority of gynecologists agree with Adair and Davis, Taussig, Kimball,

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pressed, especially at the height of a contraction. Again the cord may be compressed between the child and the birth canal. Occasionally a cord is so tightly bound around the neck or the child's body that further descent obstructs the cord circulation. Obviously the treatment is to relax the uterus, to give the woman oxygen, and to displace the presenting part upward until the fetal heart has returned to its normal rate. In cases where the scalp can be seen, increasing cyanosis, especially when accompanied with a slow heart, calls for oxygen to the mother, relaxation of the uterus, and displacement of the presenting part upward.

To relax the uterus, as has been brought out by Eastman and others, there is no drug that works as well as chloroform. To relieve apnea, as Dr. McPhail has pointed out, pure oxygen inhaled by the mother is essential. We should condemn very strongly the attempts to deliver the mother by forceps while the venous system of the child is markedly congested, especially when the cervix or birth canal is not well retracted over the head. There are too many forceps being used for the immediate extraction of the child for fetal distress.

brewer's yeast relieved the condition completely. However, yeast preparations contain not only factors of the B complex and other vitamins but amino acids. How these amino acids individually or collectively would affect these conditions remains unknown.



Fig. 1.—Patient 20, aged 85. Hyperemia, edema, and altered tissues extend laterally beyond the vulva. Pruritus present for four years. (Reproduced from 35 mm. Kodachrome picture.)



Fig. 2.—After thirty-five days of treatment on average daily intake of 25 mg. of B<sub>1</sub> and 10 mg. of B<sub>2</sub>. Slight recurrence on one occasion within past four months but completely relieved by administration of B<sub>1</sub> and B<sub>2</sub>. (Reproduced from 35 mm. Kodachrome picture.)

and others in their proposal of surgical removal or adequate vulvectomy. Norris and Block stressed by quotation the benefits gained from hormone therapy. On the premise that achlorhydria and deficiency of vitamin A resulted in the vulvar condition, Swift prescribes dilute hydrochloric acid and vitamin A. Recently Hunt describes secondary pellagrous manifestations closely resembling chronic atrophic vulvitis.

Certain reports indicate that vitamins A and D are related to infections and to leucoplakic change while vitamin C may be correlated with infections alone yet all in all these points remain unsolved. Thus, the magnitude of the field for study becomes apparent.

Special focus upon deficiencies in the components of the B complex as possible etiologic agents for certain conditions of the skin and lesions of the mucous membrane of the mouth came through the observations of Spies, Cooper, and Blankenhorn; Dabney; Landor; and Sydenstricker, Geeslin, Templeton, and Weaver. Lesions not unlike those of the lips and oral cavities were found upon the vulva, vagina, perineum, and also scrotal areas. Dabney relieved idiopathic pruritus vulvae in 4 of 8 patients with nicotinic acid. Landor relied upon riboflavin for therapeutic advantage. Elvehjem challenged with the unmodified statement that each vitamin has a very limited effect on the animal body and can be used with success only when it is lacking. Hastings, Muus, and Bessey agreed with others that the B complex is concerned with oxidation. Thiamin hydrochloride serves as a catalyst of decarboxylation, of oxidation, and of dismutation of pyruvic acid, so avers Gruzman-Barron. These and other references demonstrate that in thiamin hydrochloride deficiency, pyruvic acid content of the blood and urine increases. Pyruvic acid is also one of the by-products of certain yeast-like organisms. Such intermediary products of metabolism, as pyruvic acid, whether excreted in the urine or produced in the genital tract by the medical monilia, might create an opportunity for vulvar irritation. Such a *modus operandi* might explain certain similarities of mycotic vulvitis and chronic atrophic vulvitis.

The administration of riboflavin alone and with other factors of the same complex causes cheilosis, stomatitis, and glossitis to vanish. Sydenstricker, Kelly, and Weaver warn that under experimental conditions large amounts of nicotinic acid in the presence of deficient diets seem to increase the requirement for riboflavin and to precipitate signs of ariboflavinosis. This indicates the existence of a relationship or balance between these two components. The investigations of Spies, Bean, and Ashe; Spies, Ladish, and Bean; and Spies, Stanbery, Williams, Jukes, and Babcock leave little doubt that pyridoxine ( $B_6$ ) and pantothenic acid are essential to human nutrition. It is yet to be established whether a characteristic type of vaginitis or vulvitis may be found in patients with vitamin deficiency diseases. Moreover, the descriptions of perineal and other genital lesions are insufficiently definite to justify critical comparison with the undetermined type of vulvitis and chronic atrophic vulvitis of this series.

Rhoads brought about the disappearance of pathologic and physiologic alterations (leucoplakia) of the oral mucosa with the ingestion of large amounts of yeast. B complex deficiencies produced experimentally by Elson, Lewy, and Heublein improved only partially on thiamin hydrochloride addition, but very little with riboflavin replacement, yet

difficulties in photography. The treatment consisted solely of the administration of vitamins. Other general and all local therapy were excluded and even the diet and habits in general were unaltered intentionally.

In undertaking a study of the B complex one is faced immediately with at least 5 chemically pure substances. The order, the dosage, the route of administration, and the relationship to other components of



Fig. 4.—After forty-two days of treatment, fissures closed, hyperemia and pruritus absent. Averaged daily 50 mg. B<sub>1</sub> and 14 mg. B<sub>2</sub>. (Reproduced from 35 mm. Kodachrome picture.)

the group made for complexity of the study. Moreover, remissions or variations of chronic atrophic vulvar dermatitis and of undetermined vulvitis would nullify minor or temporary changes, presumably resulting from any therapy.

The oral route of administration was used almost exclusively for this series. Parenteral administrations might well be investigated subsequently. As has been pointed out, deficiency of thiamin hydrochloride may result from (a) inadequate diet, (b) inadequate absorption, (c) improper utilization, (d) faulty liver function, (e) vascular disease, and (f) prolonged infections.

The already heavily burdened pituitary gland received an assignment from Sutton and Ashworth to the effect that an extract of the anterior lobe of the pituitary gland caused recovery of pellagrous lesions when nicotinic acid, riboflavin, parenteral liver, and adequate diet had failed.

Morgan found that when multiple deficiencies exist unfavorable results may follow the administration of a single lacking element.



Fig. 3.—Patient 9. Edema, hyperemia, and long interlabial fissures with pruritus as principal symptom. (Reproduced from 35 mm. Kodachrome picture.)

#### PROCEDURE AND RESULTS

Obviously, the infrequency of undetermined type of vulvitis, pruritus and chronic atrophic vulvitis makes it difficult to accumulate a large number of patients for study. Through the cooperation of the entire staff it was possible to amass 22 cases in a period of approximately three years. The diagnosis was made or confirmed by other members of the staff. As a rule, the diagnosis resulted from inspection and palpation, yet in a few instances biopsies confirmed the clinical impressions. Photographic records on 35 mm. kodachrome film eliminate some error, perhaps, in respect to macroscopic superficial tissue changes subsequent to the administration of the various preparations. Reproductions in color or black and white prints from the original colored photographs have been unsatisfactory generally because of some technical

TABLE I. THIAMIN CHLORIDE ( $B_1$ ) ONLY IN VULVAR DERMATOSES

PATIENT	AGE	VULVAR DIAGNOSIS	STAGE	DAILY DOSAGE MG.	DAYS TREATED	CLINICAL AND SYMPTOMATIC RESULTS
3	47	Vulvectomy 1 yr. prior; chr. atrop. derm.	3	20	42	No change†
4	39	Chr. atrop. derm.	3	80	21	Improved symptoms only
5	49	Chr. atrop. derm.	1	10-30	42	Mod. improvement; poor co-operation
6	58	Chr. atrop. derm.	3	20-60	56	Lost leucoplakia and sympt.; vitiligo unchanged
7	57	Chr. atrop. derm.	2	20	14	Mod. improvement†
10	63	Chr. atrop. derm.	1-2	60-80	35	Improved markedly
11	47	Chr. atrop. derm.	1	20-30	56	Alleviated
12	43	Chr. atrop. derm.	1	20-40	42	Alleviated
13	42	Chr. atrop. derm.	1	20	28	Alleviated
14	43	Chr. atrop. derm.	1	10	21	Alleviated
15	47	Chr. atrop. derm.	1-2	40-80	14	Alleviated
19	64	Vulvitis (undet.)		20-80	14	Improved*
21	43	Vulvar pruritus (undet.)		5-15	56	Alleviated
22	43	Vulvar pruritus (undet.)		40	7	Improved

\*Followed with  $B_1 + B_2$ .

†Followed with TRN6P (thiamin, riboflavin, nicotinamide, pyridoxine and pantothenate combined in tablet).

TABLE II. NICOTINIC ACID OR NICOTINAMIDE ONLY IN VULVAR DERMATOSES

PATIENT	AGE	VULVAR DIAGNOSIS	STAGE	DAILY DOSAGE	DAYS TREATED	CLINICAL AND SYMPTOMATIC RESULTS
2	42	Chr. atrop. derm.	2	200 mg.	21	Relapsed under treatment
4	39	Chr. atrop. derm. with vitiligo	3	200 mg.	28	Relapsed under treatment
5	49	Chr. atrop. derm.	1	225 mg.	21	Relapsed under treatment
16	46	Vulvitis (undet.)		200-300 mg.	21	Unchanged
19	64	Vulvitis (undet.)		200 mg.	14	Unchanged

*Thiamin Hydrochloride ( $B_1$ ) and Riboflavin ( $B_2$ ) in Vulvar Dermatoses*

				$B_1$	$B_2$		
2	42	Chr. atrop. derm.	2	20-30	2-5	14	Unchanged*
8	52	Chr. atrop. derm.	2	80	10	21	Marked improvement
9	58	Chr. atrop. derm.	1-2	40-60	8-20	42	Marked improvement
16	46	Vulvitis (undet.)		80-60	20-10	21	Unchanged
19	64	Vulvitis (undet.)		80-40	20-10	21	Marked improvement
20	85	Vulvitis (undet.)		30-20	10	35	Alleviated

\*Followed by TRN6P (thiamin, riboflavin, nicotinamide, pyridoxine, and pantothenate).

in the 5 (Table II) subjected to such treatment there was hardly a suggestion that these patients were pellagrins, for the 2 with vulvitis were unaffected and the 3 with chronic atrophic vulvitis had only slight symptomatic improvement which shortly reverted to the original state.

As had been the plan, other components of the B complex were added when improvement failed or did not progress satisfactorily. Thus, riboflavin ( $B_2$ ) next came to trial in combination with thiamin hydrochloride (Table II continued). The fact that stomatitis, glossitis, and cheilosis vanish with adequate amounts of riboflavin might suggest

The general plan called for the use of thiamin hydrochloride ( $B_1$ ) orally in dosage varying from 5 to 80 mg. daily, but tending toward larger amounts. The first few patients received, often, proportionately smaller amounts, but as clinical and symptomatic reaction seemed, at times, to be related to larger amounts, more was given. Lacking clinically usable tests, guidance came from clinical and symptomatic response.

According to the usual standards, 19 of the 22 patients were free apparently of vitamin deficiency; of the remaining 3, one existed on an inadequate diet, one most likely had a faulty or inadequate absorption, and the third one suffered from a protracted and unusual infection with



Fig. 5.—Patient 15. Leucoplakic-like lesion between clitoris and urethra. (Reproduced from 35 mm. Kodachrome picture.)

multiple draining areas. Table I lists those receiving thiamin hydrochloride alone in relation to dosage, age, stage and type of lesions, length of therapy, and results. Of the 11 cases of leucoplakic vulvitis, 4 were alleviated; 1 remained unchanged; the leucoplakic area and symptoms disappeared in 1 case but the vitiligo persisted. The remaining 5 were improved from a moderate to a considerable degree. The unalleviated patients are still under observation. The word "alleviated" expresses the idea of apparent cure, but sufficient time has not elapsed to establish this point.

If the lesions were manifestations of pellagra then nicotinic acid or nicotinamide should bring about improvement if not a cure. At least



Three had definite improvement and 1 was alleviated. This special tablet is not commercially available, but its equivalent can be obtained by the administration of sufficient amounts of each of these substances.

Perhaps a better picture may be had through a composite table (Table IV) which indicates the order and type of combinations given to each patient. As one might expect the Stage I chronic atrophic dermatitis of the vulva improved more dependably than the more severe and also the more chronic ones in which considerable alteration of tissue had taken place. One of the undetermined type of vulvitis group was alleviated, 3 improved, and 1 unchanged. According to the present observations Patient 19 might attain alleviation. Possibly 2 might



Fig. 7.

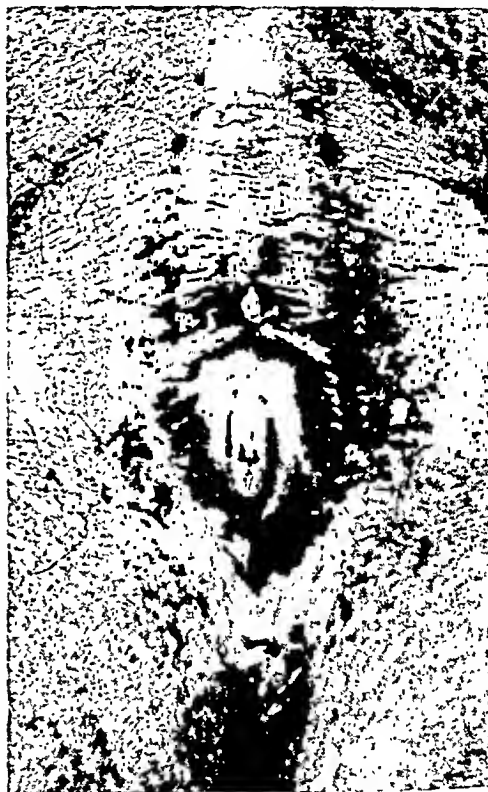


Fig. 8.

Fig. 7.—Patient 6. Biopsy of edge of perineal lesion confirmed diagnosis of leukoplakic lesion in chronic atrophic vulvitis. Note vitiligo above clitoris and on labia majora and perineum. (Reproduced from 35 mm. Kodachrome picture.)

Fig. 8.—Leukoplakic lesion and pruritus absent but vitiligo and atrophic change unaltered. Treated fifty-six days, average daily intake 40 mg. of B<sub>1</sub>. (Reproduced from 35 mm. Kodachrome picture.)

be classed as chronic atrophic dermatitis, but infections resulting probably from the trauma of scratching made it obligatory to place them in the class of undetermined. Pruritus is entirely subjective and hence not reliably evaluated by observations. Such symptoms lend their course to many influences.

Some patients have been maintained on one or another of the vitamin B complex for considerable periods without evidence of intoxication, but further observations are imperative to verify the safety of this practice. If such large amounts are actually necessary, perhaps the

that this factor should be tried individually; and later a trial will be given to it alone. From these 6 cases, 2 were refractory to this management; 1 with a chronic atrophic vulvitis and 1 with undetermined vulvitis. One undetermined vulvitis was alleviated while 1 improved. Two cases of chronic atrophic vulvitis showed improvement. These 3 improved cases now appear to be well on the way to an apparent cure. One patient, aged 85 years, had a niece 64 years of age and both had an unexplained vulvitis, which was rather similar, yet they had apparently adequate diets and lived in different communities.



Fig. 6.—Condition and symptoms alleviated in fourteen days. Average daily intake of  $B_1$  60 mg. (Reproduced from 35 mm. Kodachrome picture.)

To combine the other three factors with  $B_1$  and  $B_2$  might shorten the study. A tablet with five factors was available. It contained 5 mg. of thiamin hydrochloride, 5 mg. of riboflavin, 25 mg. of nicotinamide, 5 mg. of pyridoxine ( $B_6$ ), and 25 mg. of calcium pantothenate.\* The daily dosage varied from 3 to 6 tablets but was usually 4. Most of the patients were given additional  $B_1$  to make a daily total of  $B_1$  from 60 to 100 mg. Seven patients on this combination gave varied and unexplained responses (Table III). Both patients who had had recurrence after vulvectomy, improved symptomatically, while the tissue changed only by regression of hyperemia and healing of fissures, but the atrophic state and vitiligo persisted. One patient has been a frank failure so far.

\*This and the other vitamin preparations were supplied by Merck & Company.

action is pharmacologic rather than strictly a vitamin response. If large doses are required the mixed proprietary products on the market would appear impotent or of very limited value because of their minute amounts, but proof is not yet forthcoming.

### SUMMARY

These observations are presented for their scientific value alone. The data show that management as outlined above did not eradicate vitiligo or correct advanced (Stage 3) chronic atrophic dermatitis of the vulva although symptoms may be partially or completely relieved and fissures and leucoplakic areas may disappear. On the other hand the first stage of chronic atrophic vulvitis and certain other types of undetermined vulvitis may vanish with the administration of thiamin hydrochloride, thiamin hydrochloride and riboflavin, or multiple factors of the B complex. This difference may be anticipated because response should be more likely before extreme tissue damage has occurred. When prescribing factors of the B complex, sufficient amounts are indicated and a balance or relation of the factors may be necessary.

A tendency existed for recurrences in a few of the alleviated patients, possibly because of premature withdrawal of the vitamins, possibly because of some imbalance in the metabolism other than a deficiency disease process, or possibly because of some other state. Small doses may be needed for an indefinite period for some who responded to this management, but as yet a conclusion cannot be made.

Although alleviations (presumable cures) transpired under the administration of factors of the B complex, these conditions have not been classed as manifestations of deficiency diseases.

Moreover, one should not attempt such therapy for chronic atrophic dermatitis of the vulva unless one is prepared to observe and follow the case for a sufficient length of time in order to establish satisfactory benefit to the patient or institute appropriate therapy such as vulvectomy, lest a malignancy develop. Such management is not yet endorsed except for individuals in such poor health that surgery would not or should not be done and for those cases of vulvitis for which an established therapy is wanting. If the distress of chronic irritation can be relieved perhaps the incidence of malignancy might be reduced.

The need for more and properly controlled studies for evaluation of these vitamins becomes evident especially to guard against their misuse and abuse as well as to render better care for patients. Caution is stressed in the use of the vitamins.

Appreciation is expressed for the thoughtful cooperation of the members of the department in this investigation and also for the valuable aid of Merck & Company in supplying the vitamin preparations.

### REFERENCES

- (1) *Adair, F. L., and Davis, M. E.*: Surg., Gynec. & Obst. 61: 433, 1935.
- (2) *Bonney, V.*: Proc. Roy. Soc. Med. 31: 1057, 1938.
- (3) *Dabney, M. Y.*: South. Surg. 8: 232, 1939.
- (4) *Elson, K. O., Lewy, F. H., and Heublein, G. W.*: Am. J. M. Sc. 200: 757, 1940.
- (5) *Elvehjem, C. A.*: Physiol. Rev. 20: 249, 1940.
- (6) *Guzman-Barron, E. S.*: Bol. Soc. Quim del Peru 7: 7, 1940.
- (7) *Hastings, A. B., Muus, J., and Bessey, O. A.*: J. Biol. Chem. 129: 295, 1939.
- (8) *Hesseltine, H. C.*: AM. J. OBST. & GYNEC. 34: 855, 1937.
- (9) *Hunt, E.*: Diseases Affecting the Vulva,

TABLE III. COMBINATION OF CERTAIN B COMPLEX FACTORS ONLY IN VULVAR DERMATOSES

TRN6P (Each tablet contains thiamin 5 mg., riboflavin 5 mg., nicotinamide 25 mg., pyridoxine 5 mg., Ca. pantothenate 25 mg.) - X

PATIENT	AGE	VULVAR DIAGNOSIS	STAGE	DAYS TREATED	CLINICAL AND SYMPTOMATIC RESULTS
1	68	Chr. atrop. derm.; vulvectomy 2 yr. prior	3	91	Symptoms improved; tissue unchanged
2	42	Chr. atrop. derm.	2	35	Unchanged
3	47	Chr. atrop. derm.—Perin.; vulvectomy 1 yr. prior	3	84	Symptoms improved; tissue unchanged
7	57	Chr. atrop. derm.	2	98	Improved
14	43	Chr. atrop. derm.	1	42	Alleviated
17	39	Vulvitis (undet.)		42	Improved; poor cooperation
18	31	Vulvitis (undet.)		28	Improved; poor cooperation

X = 3 to 6 tablets daily and usually enough more thiamin added to give total of 60 to 100 mg. daily.

TABLE IV. TREATMENT BY VARIOUS FACTORS OF THE B COMPLEX

PATIENT	AGE	STAGE	N***	B <sub>1</sub> †	B <sub>1</sub> & B <sub>2</sub> ‡	TRN6P§	DAYS TREATED	CLINICAL AND SYMPTOMATIC RESULTS
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*Chronic Atrophic Vulvar Dermatitis*

1	68	3**	*			1	98	Sympt. slightly impr.; tissue unch.
2	42	2	1		2	3	70	Unchanged
3	47	3**		1		2	126	Symptoms impr.; tissue unch.
4	39	3	1	2			49	Impr. symptomatically only
5	49	1	2	1-3			63	Improved
6	58	3		1			56	Lost leucoplakia and sympt.; vitiligo unchanged
7	57	2		1		2	112	Improved
8	52	2			1		21	Improved markedly
9	58	1-2			1		42	Improved markedly
10	63	1-2		1			35	Improved markedly
11	47	1		1			56	Alleviated
12	43	1		1			28	Alleviated
13	42	1		1			28	Alleviated
14	43	1		1		2	63	Alleviated
15	47	2		1			14	Alleviated

*Vulvitis (Undetermined Type)*

16	46		1		2		42	Unchanged
17	39					1	42	Improved; poor cooperation
18	31					1	14	Improved; poor cooperation
19	64		2	1	3		49	Improved markedly
20	85				1		35	Alleviated

*Pruritus*

21	43			1			56	Alleviated
22	43			1			7	Improved; poor cooperation

\*1, 2, 3, etc., order in which used. \*\*Vulvectomy previously for chronic atrophic vulvar dermatitis. \*\*\*N, Nicotinic acid or nicotinamide.

 †B<sub>1</sub> Thiamin Hydrochloride.

 ‡B<sub>2</sub> Riboflavin.

 §TRN6P (Each tablet contains thiamin 5 mg.; riboflavin 5 mg.; nicotinamide 25 mg.; pyridoxine [B<sub>6</sub>] 5 mg.; and Ca. pantothenate 25 mg.) usual extra B<sub>1</sub> given.

## Special Article

### DEVELOPMENTS AND TRENDS IN GYNECOLOGY\*

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I SHALL not attempt in a short address to cover the history of gynecology. It would be a futile endeavor, and besides I am sure that you are all familiar with the high lights of the history of your science and art. My task will be different. Taking gynecology as my subject, I would like to make a few general historical remarks and would like to show you that there are two aspects of the history of medicine. Unless we consider them both, we shall never attain to a comprehensive picture of developments. There are actually two histories of medicine. One is the history of medical science. It teaches how man gradually discovered the structure of the human body, the function of its organs, disease mechanisms, methods to diagnose disease conditions, to evaluate them in making a prognosis, and finally methods of treatment. The more knowledge man had, the more effective his weapons became in the prevention and cure of illness. This, however, is only one side of the picture, and there is another aspect to it, the social and cultural history of medicine. Knowledge alone is not enough. It does not become effective unless we are able to apply it. Society must be ready to accept the physician's advice, and here we find that religious and philosophic views, social and economic conditions had a tremendous influence and largely determined success or failure of medicine.

There is another point that must be taken into consideration. Scientific research was applied to subjects that seemed important at the time. Valuations changed a great deal and were also determined by non-medical factors. Modern pediatrics could not develop before chemistry had reached a certain level, but it could not develop either before it had been recognized that the child is more than a small-sized adult, and before the position of the child in society had changed. This likewise was the case with gynecology. The attitude of society toward woman and her position in the social structure were just as important factors in the history of gynecology as medical science. I would like to illustrate this by going with you rapidly through the various periods of history.

A determining point in the history of gynecology is to be found in the fact that sex plays a more important part in the life of woman than in that of man, and that she is more burdened by her sex. Nature has imposed menstruation upon her, the long period of pregnancy, the pains of childbirth, and the period of nursing. This explains two basic attitudes. Woman is periodically weakened by her sex life and in need of protection. She becomes dependent on somebody else, and this opens the door to exploitation. The history of exploitation of woman by man is endless. Whoever has traveled in the eastern Mediterranean countries

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St. Louis, 1940, The C. V. Mosby Co. (10) *Hunt, E.*: Lancet 1: 592, 1936. (11) *Kimball, D. C.*: Univ. Hosp. Bull., Ann Arbor 1: 49, 1935. (12) *Landor, J. V.*: Lancet 1: 1368, 1939. (13) *Montgomery, H., Counsellor, V. S., and Craig, W. M.*: Arch. Derm. & Syph. 30: 80, 1934. (14) *Morgan, A. F.*: Science 93: 261, 1941. (15) *Norris, C. C., and Block, F. B.*: Am. J. M. Sc. 200: 551, 1940. (16) *Rhoads, C. P.*: Proc. Inst. Med., Chicago 13: 198, 1940. (17) *Spies, T. D.*: Tr. & Studies Coll. Physic., Philadelphia 8: 12, 1940. (18) *Spies, T. D., Bean, W. B., and Ashe, W. F.*: J. A. M. A. 112: 2414, 1939. (19) *Spies, T. D., Cooper, C., and Blankenhorn, M. A.*: J. A. M. A. 110: 622, 1938. (20) *Spies, T. D., Ladisch, R. K., and Bean, W. B.*: J. A. M. A. 115: 839, 1940. (21) *Spies, T. D., Stanbery, S. R., Williams, R. J., Jukes, T. H., and Babcock, S. H.*: J. A. M. A. 115: 523, 1940. (22) *Sutton, D. C., and Ashworth, J.*: J. Lab. & Clin. Med. 25: 1188, 1940. (23) *Swift, B. H.*: J. Obst. & Gynaec., Brit. Emp. 43: 1053, 1936. (24) *Sydenstricker, V. P., Geeslin, L. E., Templeton, C. M., and Weaver, J. W.*: J. A. M. A. 113: 1697, 1939. (25) *Sydenstricker, V. P., Kelly, A. R., and Weaver, J. W.*: South. Med. J. 34: 165, 1941. (26) *Taussig, F. J.*: Diseases of the Vulva, Gynecological and Obstetrical Monographs, New York, 1931, D. Appleton-Century Co., Vol. XIII. (27) *Taussig, F. J.*: AM. J. OBST. & GYN. 31: 746, 1936. (28) *Wilson, W. M.*: Northwest Med. 33: 268, 1934.

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## DISCUSSION

DR. FRED J. TAUSSIG, St. Louis, Mo.—I have for many years sought to relieve cases of leucoplakic vulvitis and pruritus of the vulva by various nonsurgical procedures. Ointments were found to be of little, even palliative, benefit. Ovarian therapy, on the other hand, particularly since we have obtained more powerful products, such as stilbestrol, seems in a limited group of cases to have not only caused relief of symptoms but also to produce temporarily marked improvement in the vulvar skin. Those with less advanced lesions, in the so-called hypertrophic stage of leucoplakic vulvitis, show a higher percentage of relief.

Many years ago I had a patient with well-developed kraurosis, who refused operation and later went to a general practitioner who put her on a low-protein, high carbohydrate diet with complete relief of symptoms and marked local benefit. Through other members of the family I learned that she remained well for three years, when she died suddenly of apoplexy. Many of these women are advanced in years and not good operative risks, so that a nonsurgical treatment is worth consideration.

I have tried Swift's method of giving dilute hydrochloric acid with vitamin A in four or five cases but without any success. Thus far my experience with vitamin B complex is too recent to justify any opinion as to its efficacy.

A definite leukokraurosis is so frequently the forerunner of cancer, that surgical ablation of the vulva and, if necessary, of the perianal skin, should in my opinion alone be considered. In my recent report on cancer of the vulva, I discussed several cases of leucoplakic vulvitis, that were not kept under close observation and later returned with a well-developed cancer. Any nonsurgical procedures therefore that give temporary relief may lull the patient into a state of false security. Such individuals must be told to report for re-examination every four to six months for the rest of their lives, since the atrophic brittle skin is constantly subject to minute abrasions and cracks, from which a malignancy may develop.

Of course we know little or nothing about the whys and wherefores of vitamin therapy and all apparent results must be analyzed with the greatest skepticism, but the history of medicine is full of examples of a proved therapeutic agent found long before the manner of its action has been discovered. In view of the relative infrequency of these chronic atrophic lesions of the vulva, I would suggest that in the earlier cases a more extensive trial be given of this method of treatment with vitamin B complex in the dosage recommended by Dr. Hesselstine, so that we can arrive at some opinion of its value in the course of the next five years.

(The remaining papers presented at the Sixty-Sixth Annual Meeting of the American Gynecological Society will be published in the November issue.)

Childbirth was considered a physiologic process and was therefore not an object of medicine. In primitive society a woman, when her hour had come, went into the bushes or to the river, and came back after a while with the newborn infant. If help was needed, it was given by a fellow woman who had gone through this experience herself and therefore knew about it. This still happens today all over the world. And when women began to give this aid professionally, they became midwives. The institution of midwifery has played an extraordinarily important part in the history of medicine. Until a few centuries ago, the midwife was the gynecologist and obstetrician of society. She had empirically acquired knowledge and skills, and in addition was the confidante of women. She, and not the physician, was consulted by women in all matters of sex.

Having been trained in Europe where the institution of midwifery is still firmly established, I have a high respect for the work of these women. I have seen them in action in mountain villages of the Caucasus and among African tribes. As long as society cannot provide a trained obstetrician for every woman, the midwife still has an important part to play, and there are conditions where she can achieve more than the physician. She has more time to spend with the woman in labor, and is frequently closer to the people, one of them, speaking their own language and familiar with their customs.

We do not know when gynecology became a part of medicine. No date can be set for it. As soon as man began to observe symptoms of disease and to reason about them, he saw that women were suffering from pains peculiar to them, from fluxes, discharges, and swellings, that their periods were irregular and that childbirth was not always a physiologic process. Egyptian papyri and Babylonian cuneiform tablets all mention gynecologic symptoms and treatments. Magic took a relatively important part in this field of medicine. Amulets were worn. No Egyptian woman would enter labor without having a statuette of the hippopotamus-shaped goddess Thoris near by. Amulets are still worn by women in childbirth today. The old idea that in such moments people are the easy target of evil spirits still persists. From Herodotus we know that Egyptian medicine at his time was highly specialized, that there were specialists for every organ and every disease. We do not hear of specialists for the female organs, for the good reason that these organs and the diseases of women were the midwife's domain. She was the specialist.

In ancient Greece the social position of woman varied a great deal according to tribes. Among the Dorians of Sparta girls took an active part in the physical exercises of boys. They were trained to be mothers of soldiers. Conditions were different among the Ionians where the girl grew up in the house, was veiled in the streets and was married by her parents. She attended to the household duties, and the midwife was her gynecologist.

In the fifth and fourth centuries B.C., there was a movement toward emancipation. Plato postulated equal rights and equal duties for men and women including the duty to go to war. Aristotle considered woman an inferior being, an incomplete man, but he too wanted to see her social position improved. Increased attention was paid to women and their ailments, and the Hippocratic writings reflect this trend. Physicians as a rule did not treat gynecologic diseases, but they studied and discussed them. More and more frequently midwives consulted with physicians in difficult cases. From Hippocrates to Alexandria to Rome

remembers the familiar sight of a woman marching with heavy loads on her head and arms, followed by her husband and lord riding comfortably on a donkey and smoking a cigarette. Even in our own society we discriminate constantly against women, paying them lower wages than men for equal work. We discriminate against married teachers and against women students and physicians even in our own medical schools and hospitals.

On the other hand, woman by giving birth to life became an object of worship. She is fertile like the soil. It was known that seed was needed for the plant to grow, but wherever the soil was fertile vegetation was found. The mystery of creation takes place in woman as it does in nature. Nature was worshiped, and so was woman. The Great Mother was a deity found in the earliest civilizations. Neolithic statuettes have been excavated representing a woman that consists of nothing but sex, and there can be hardly any doubt that they represent a deity. In some tribes the dead were buried, their heads covered with cowry shells. The shells were the symbol of the female genital organs, of the door to life. The shell caps were meant to help the dead in coming back to life again. This function of woman as the creator of life gave her prestige, and power at times, which explains why matriarchy was the social organization of many early tribes.

The fertility of man was rarely questioned, and even today when a family has no children the wife is suspected first, and it is difficult to convince a husband that he may be responsible for the condition.

The fact that the mystery of creation takes place in woman led to the view that the womb must be an organ of a special kind. The uterus was frequently viewed as a living organism of its own, endowed with independent motions, with desires and whims. One of our oldest medical documents, the gynecologic papyrus of Kahun written in the third millennium B.C. describes the uterus as being irritated or sluggish or wandering to places where it does not belong. All these conditions were considered to be causes of disease. The word hysteria that we still use means nothing else but the disease of the hystera, which is the Greek word for uterus. In a medieval incantation that I found in a tenth-century manuscript the exorcising priest addresses himself to the uterus, conjuring it to remain in the place destined for it by God and not to wander through the human body causing disease. In votive offerings the womb was frequently represented as an animal, chiefly as a toad. Even in rational therapy certain procedures such as fumigations with odoriferous drugs were meant to "please" the organ.

Because sex played such an important part in woman's life, and because new life came from her, more taboos were imposed upon her than upon man. In all ancient cults woman was considered unclean during her periods, during childbirth and in childbed. As long as she was unclean, she was not permitted to enter the temple, and her condition was considered contagious until she had undergone purification. This gave her an isolated position in society. The concept of cleanliness was purely spiritual, but it had hygienic consequences in that it protected woman against sexual intercourse during menstruation and during the period of involution. These old views, familiar to us from Leviticus, are still alive, not only among Jews but in the whole Mohammedan world. I heard in Bosnia that women there are not allowed to give birth to children in the house, since this would make it impure. They go to the stables where the child is born between a cow and a goat, and infections result quite frequently.



There was woman-worship in the Middle Ages too. There was a cult of Mary, but Mary was a virgin who had conceived without sin. There was a cult of woman in chivalry, but it was short-lived, had pagan elements, and was limited to a small group. Throughout the Middle Ages woman was relegated to the home and kept subservient to man.

Such conditions were not favorable for the development of gynecology, and hardly any progress was achieved during the period. Practices followed traditional lines and consisted of ancient reminiscences. Gynecology and obstetrics were in the hands of midwives. The *Mulieres Salernitanæ* were midwives, specialists in the treatment of women's ailments. Literature consisted mostly of catechisms, from that of Mustio in the sixth century A.D. to the Rosengarten of Rösslin in 1513.

A revolution was created in the Renaissance in this, as in other cultural fields. A new world developed in Western Europe which was very different from the static world of the Middle Ages with its rigid regulations. The new world appealed to the individual in man and called for free competition and free initiative. The attitude toward woman changed, and voices were heard calling for her liberation. The great humanist Erasmus of Rotterdam in one of his Colloquies has a woman say: "Men are tyrants . . . They use us as toys . . . They make us their laundresses and cooks and take great care to exclude us from all other functions. Let them keep for themselves the tasks of government and war, but the mother should at least have a vote when it comes to establishing her children." Another humanist, Cornelius Agrippa, in a Latin *Disquisition on the Nobility and Preexcellence of the Female Sex*, published in Antwerp in 1529, went even further when he said: "Acting against all divine law, violating with impunity natural justice, the tyranny of man has deprived woman of the liberty with which she was endowed at birth. . . . As a child she is kept idle in the home. As if she were unable to attend to any higher function she is not permitted to touch anything but needle and thread." Yet she has a claim to rights. Her part in the bearing of children is much more important than that of man. She nourishes those fragile little creatures and attends to their development. And is she not just as intelligent as the other sex? She has even more insight and acuteness of spirit. Guided by an instinct which is a privilege of her nature, she often sees things more correctly than philosophers and scholars.

With this scientific and social background gynecology could not but progress. In the sixteenth century the foundation of a new descriptive, systematic human anatomy was laid. All the anatomists of the time studied the female organs. Leonardo's drawings of the child in utero were the first to break a long tradition of diagrammatic pictures that illustrated catechisms from Mustio on. Vesalius observed that the pelvic bones do not separate in childbirth. Falloppio described the tubes; Aranzio observed deformities of the pelvis.

On the basis of this new anatomy a new surgery was born, and this immediately benefited obstetrics and gynecology. In France, Ambroise Paré became not only the "Father of Surgery" but was also greatly interested in obstetrics and called himself not only a surgeon but also an *accoucheur*. He and his disciple Guillemeau practiced podalic versions, induced premature labor in cases of hemorrhage, and sutured the perineum. Cesarean section had been practiced on the dead for centuries, ever since an old Roman law had prescribed that no pregnant woman might be buried without having the child removed. But now the operation was practiced on the living woman, not by sow gelders as the

and Soranus women's diseases appear in the medical literature, and there is no doubt that the Greek and Roman physicians had considerable knowledge in the field. Many symptoms have been described correctly, and diseases were treated with diets and drugs. Operations were performed, such as embryotomy and the podalic version.

One point must be discussed particularly, because it presents some problems, namely, the ancient attitude toward abortion. The Hippocratic Oath forbids the physician to practice abortion. This is a rather startling prohibition because we know that abortion was practiced very frequently throughout antiquity and that it was recommended by philosophers as a method of regulating the population. Weaklings and crippled infants were destroyed without hesitation, and it is difficult to understand why there should have been any inhibition in the case of abortion. I know only two possible explanations. The Oath seems to be a very old document reflecting conditions when medicine was a secret family lore. The Oath may have been close to certain religious movements, such as Orphism, which forbade the destruction of life in any form. Another possibility is that the physician was forbidden abortion because he should leave it to the people whose business it was, namely, the midwives, just as the Oath forbade the physician the practice of surgery.

The situation changed completely with the advent of Christianity. Christianity came into the world as a religion that promised healing and redemption, both spiritually and physically. It addressed itself to the weak and sick, to the cripple and sinner, and it gave the sick man a preferential position in society. It was declared the duty of society to attend the sick, and nursing developed as never before. The attitude toward pagan medicine was by no means friendly in the beginning. As a religion, Christianity was primarily interested in the health of the soul, and a great deal of interpretation was required to justify care of the body, and to reconcile the new creed with ancient science.

The attitude toward woman was by no means favorable for the development of gynecology. Man and woman were declared equals before God, spiritually, in the hereafter, but otherwise woman was considered an inferior being. Man was made from earth, but woman from man's rib. Sin had come into the world through Eve. Her sin was responsible for the pains of love and for the pains of childbirth. A church father called woman *janua diaboli*, the door to hell.

These views also influenced the attitude toward sex. The Greeks had taken sexual intercourse for granted and had looked at it as a physiologic process that was recommended sometimes for reasons of hygiene. Christianity considered sexual intercourse sinful unless it was performed by married persons with the definite purpose of procreating children. Origenes went so far as to postulate that it should be performed dispassionately, and that even then it should not take place in a room where people pray. The soul counted and salvation was the purpose of life. Abortion was considered murder of a particularly vicious kind, because it prevented a human being from being baptized. Faced with the alternative of saving mother or child, the physician was to sacrifice the mother without hesitation since the mother was already baptized and prepared for the hereafter, while the unbaptized child would be relegated to limbo. Contraception was even worse because it prevented the creation of a human being. Christianity set rigid taboos on sexual matters, under which the Western World had to suffer for a long time.

midwives of the period, such as Louise Bourgeois, Marguerite du Tertre, and Justine Siegemundin. They were skilled obstetricians, and their books were widely read.

In the eighteenth century pathology became anatomic. From Vesalius on, pathologic changes had been observed in organs and such findings were collected by Théophile Bonet in his *Sepulchretum* of 1679. It was Morgagni, however, who in 1761 laid the foundation of modern pathologic anatomy and created the method of pathologic research that was to be followed from then on. In the third volume of his *De Sedibus et Causis Morborum* he discussed pathologic changes of the female genital organs. In the following years many dissertations were written on such subjects, and the method of Morgagni was continued by Bichat and Virchow who traced anatomic changes in the tissues and in the cell. On the basis of these studies the various gynecologic diseases could be sharply defined, and most disease entities that we recognize today were established during the nineteenth century in pursuit of this trend.

As soon as pathologic anatomy was established, a new task was set for clinical diagnostic. Its purpose became to recognize anatomic changes on the living organism with physical methods. This is why percussion and auscultation were introduced at that time and became chief methods of physical diagnostic. It was Lejumeau de Kergaradec who had the brilliant idea of applying Lacunee's auscultation to watch the heartbeat of the fetus.

The eighteenth century was an international century. Every country made its contribution to gynecology. In England William Smellie and William Hunter produced their superb atlases of the pregnant uterus. Special lying-in hospitals were created in every country. They not only improved the conditions of women in childbirth, but improved also the educational facilities for midwives.

In the nineteenth century therapy became anatomic, and this explains the tremendous development of surgery. General anesthesia, antisepsis, and asepsis broke the age-old bonds that had impeded the progress of surgery. Anesthesia and asepsis were found because medicine had reached the point at which surgery was no longer the ultimum refugium to which resort was taken when all other methods had failed, but had become a primary goal. Surgery revolutionized gynecology and obstetrics. Major abdominal operations could be performed now. Large tumors could be removed without danger to the patient, and cesarean section was no longer an act of desperation. The development of surgery also created a new type of hospital, and the number of deliveries that took place in hospitals increased considerably. In this great development American surgeons have played a very important part, and I need only remind you of the names of Ephraim McDowell and James Marion Sims.

Today a cycle has come to an end. The anatomic approach inaugurated in the Renaissance has been applied to one medical field after another, and today we are in a physiologic era. Physiology is in the foreground of all considerations. We no longer operate for a retroflexion merely because the uterus does not hold the position prescribed for it by the textbooks. Function is being considered first of all. New physiologic discoveries, particularly that of hormones and vitamins have stimulated both gynecology and obstetrics.

I cannot discuss the recent developments, and I need not do it because the gynecology that you practice today represents the experience of the

legend had it, but by the ablest surgeons. Guillemeau describes five cases of cesarean section, two of which he performed himself in the presence of Paré, while three were performed by others. They were all fatal. The time was not yet ripe for major abdominal surgery.

Midwives were still the chief practitioners of obstetrics and gynecology, but they were pledged frequently to call the surgeon in difficult cases. Many were in the service of the cities and their profession was regulated strictly. They were examined and had to follow fee schedules. In the sixteenth century the city of Ratisbon established old age and disability pensions for midwives.

The seventeenth century was a period of great tensions and contrasts. While Descartes inaugurated a period of rationalism, the Counter-Reformation was launched, religious intolerance flourished, Campanella was tortured, and Giordano Bruno burned at the stake. At the same time, when absolutistic government prevailed in France, Spain and a number of other countries, democracy developed in England and Holland. In France women became more and more articulate, claiming access to higher education. It was the time when Molière wrote his *Femmes Savantes* and his *Précieuses Ridicules*. The Salon flourished in France where scientists were invited to present their discoveries before an audience of men and women. It was a mechanical age. Mathematics were highly cultivated, and the names of Descartes, Pascal, Leibnitz, and Newton remind us of the great progress achieved in this field. In physics, dynamics and particularly hydrodynamics were in the foreground. Practical necessities forced scientists to take up these studies. Waterways were the chief highways of traffic. The journey from Constantinople to Venice was three times longer by land than by sea, and while the two-wheeled oxcart could not carry more than 2 tons of goods, the average-sized ship transported more than 600 tons. All these trends reflected themselves in medicine, and in gynecology also.

In the seventeenth century, anatomy became *anatomia animata*, dynamic anatomy. William Harvey founded a new physiology, but he was an embryologist also. Embryology is another form of dynamic anatomy. Embryologic studies greatly benefited gynecology. Van Horne declared that the female testicles contain ova. Steno gave the ovaries their name, and de Graaf wrote a classical monograph on the female genital organs, in 1672. In 1677 the spermatozoa were seen.

France had its great century, the Siècle de Louis XIV, and the leading gynecologist was Mauriceau whose textbook, first published in 1668, was used all over Europe.

Holland had at that time its great period of expansion and colonization. More than any other country it developed its waterways. Henrik van Deventer was a goldsmith who became a physician; being interested in mechanical problems, he entered the field of orthopedies. His wife was a midwife, and he became interested in the architecture and mechanics of the pelvis, a subject to which he made important contributions. It is not astonishing that this mechanical age produced the most important tool in obstetrics, the forceps. Invented by a barber surgeon Chamberlen, it was kept a family secret, was discovered independently by Jean Palfyn, and was approved by the Paris Academy in 1723.

The education of midwives was improved. In 1630 they were given regular courses in France at the Hôtel-Dieu. In Germany they were instructed by the municipal surgeons. Great names appear among the

I have shown you that the gynecologist had two ancestors. The surgeon was his father, the midwife his mother. From the father he inherited techniques, knowledge, and skills; from the mother he received in addition the human touch. Like the midwife of old, he must be the confidant of women who consult him whenever they are in trouble, whether their ailments are organic or not.

In gynecology and obstetrics as in every other field of medicine, the urgent problem of our day is to make whatever knowledge we have available to all who need it. Great progress has been achieved and many human lives are being saved that would have been lost irrevocably only yesterday. But we all know that conditions could be better than they are. In spite of all progress, with all the knowledge and equipment we possess, we still lose in this country annually about 9,000 young mothers from the results of pregnancy and childbirth, and we lose many of them needlessly. Every year more than 180,000 young women go through the trying period of pregnancy and childbirth and the result is a dead child or one that will die during his first year of life. Our task is not yet solved. Science and technology developed more than ever before. As a result medicine progressed, the structure of society changed, and so did the position of women in it. Conditions are totally different today from what they were one hundred or only fifty years ago. It is obvious that adjustments must be made.

You as individuals and as a group are leaders in your field. Through your researches you have advanced the science of gynecology considerably. Your society was founded in 1876 and when you look back you can be justly proud of your achievements, but you must remember that since 1876 the world has changed a great deal. New social problems have become very acute, and I am sure that in this field also the country is looking to you for leadership.

last fifty years. I would like to draw your attention, however, to the social history of the period, an aspect that has been frequently underestimated.

The Industrial Revolution was the event that had the most profound influence on the entire nineteenth century and on our days too. Industrialization created employment not only for men but also for women and children. Women entered the process of production in increasing numbers. The textile industries were built up almost entirely with women labor, but women worked also in mines underground and in other industries until factory legislation stopped some of the worse abuses. As a result, health conditions deteriorated, particularly among women. The population increased, especially the indigent population that lived crowded in slums, in the suburbs of cities, under atrocious hygienic conditions. We often forget that at the time when the French clinic flourished and modern medicine was making tremendous progress, health conditions were exceedingly bad. The reports of Villermé in France, of 1840, and of Chadwick in England, of 1842, speak an eloquent language.

Industrialization had other results. Women were doing men's work. The development of industry would have been impossible without them. It was nothing but justice that they should have been entitled to share not only man's labor but also his rights, that they should have had equal opportunities of education and that the professions should be open to them. It was felt that they should have a voice in the administration of the commonwealth. A long struggle ensued against the vested interests of men, a struggle that was not without dramatic episodes. Women won their case in most civilized countries, at least to a certain extent. Their gains are now challenged in the Fascist countries.

This whole development had some definite bearing on gynecology. Woman may have equal rights and all occupations may be open to her. Modern society needs her labor, but nevertheless she remains woman and carries the additional burden of her sex. She creates commodities and services, but she creates, in addition, our children. She is therefore entitled to added protection. She cannot be considered free and equal as long as pregnancy means loss of a job. If she is to be truly free and equal, she must be guaranteed regular vacations on full pay and the rest she needs during pregnancy and after childbirth without loss of wages. Maternity homes, nurseries, and all other means for the protection and restoration of health must be made easily available to her.

The strain of life in an industrial society weighs heavily on the working girl and woman, and maladjustments of some kind or another make them seek the advice of a gynecologist. My colleague Sellheim in Leipzig used to say that a woman's period is like a clock. Whenever something goes wrong in that complicated mechanism, the clock immediately reveals it by being fast or slow or otherwise wrong. Gynecologic complaints drive a woman to the physician, but her ailment may not necessarily be the result of a gynecologic disease. A psychologic or social maladjustment may be responsible for it. A gynecologist who would be nothing but a surgeon would be utterly helpless in such a case.

Gynecology, as the word indicates, is the science of woman in health and disease, of her physiologic and pathologic processes and of all problems peculiar to her. This requires that the gynecologist be not only a scientist but also have a broad psychologic and social approach to his problems.

## Second American Congress of Obstetrics and Gynecology

**I**N RESPONSE to a country-wide demand, a second Congress devoted to this important field of medicine will be held in St. Louis on April 6 to 10, 1942. The success of the previous gathering in Cleveland in 1939 may be measured by the attendance of several thousand persons, including physicians, nurses, public health workers, and hospital administrators. The program of the previous Congress embraced features appealing to each and all of these varied groups and that being prepared for the coming one will be equally catholic in its presentation.

The good health and welfare of womankind constitutes an outstanding asset in every nation and all effort should be made to preserve her important functions. This country has been held up in the past as irresponsible in this respect, whether justly or unjustly. It may be stated, however, that within recent years great and noteworthy progress has been demonstrated, as is evidenced by the lowered mortality and morbidity rates associated with childbearing and the reduction of neonatal and early infancy deaths, throughout almost all parts of the United States.

There are still many problems to be solved, medical, economic and social, and much more can be accomplished through the medium of congresses such as this and the opportunities thus afforded for the discussion and dissemination of ideas and proposals for further advancements in this field.

Future issues of the JOURNAL will present additional details of the program and other information relative to this important gathering.

## Editorials

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### Depriving the Infant of Its Placental Blood

**W**HETHER the time of clamping the umbilical cord is of significance to the baby has been a controversial subject for many years. Older workers advocated late ligation in the belief that the greater amount of blood flowing to the baby was beneficial and the initial weight loss of the infant was less than after late clamping. Recently early clamping has been practiced by those who advocate the use of placental blood for "blood bank" purposes but, even when the blood is not collected, the practice is a common one.

The amount of blood in the placenta is large, averaging over 100 c.c.\* In occasional instances it is over 200 c.c. About 50 per cent of this blood flows into the baby in the first minute after delivery and over 90 per cent in the first ten minutes. Since the average blood volume for newborn infants is about 500 c.c., it is apparent that the placenta is capable of raising the blood volume by about 20 per cent. It is of some interest to note that blood continues to enter the infant's circulation after pulsation of the cord has ceased.

Recently DeMarsh, Alt, Windle and Hillis† undertook a study of the effect of early clamping of the cord on the red corpuscle count and the hemoglobin content of the blood during the first week of life. They found that, in the group where the cords were ligated early, the red corpuscle count and the hemoglobin were, on the average, lower than in infants whose cords were clamped after the placentas had separated. The reticulocytes showed a higher average value when early ligation was practiced, suggesting a greater demand for blood in this group than where clamping was delayed.

These authors point out that the placental blood normally belongs to the infant and that its deprivation amounts to the equivalent of a rather severe hemorrhage. The loss of blood may be a serious matter for the prematurely born infant, but even in the full-term infant the blood received from the placenta may be an important source of iron for the manufacture of hemoglobin later on. During the physiologic anemia which develops in the first two to three months of life, hemoglobin is broken down, liberating iron. This iron is not lost from the body but is stored in the tissues and is used in the synthesis of hemoglobin as needed. It is quite possible that loss of placental blood is a factor predisposing to anemia during later infancy.

The study of DeMarsh, Alt, Windle and Hillis offers convincing evidence in favor of late clamping of the cord. The use of placental blood for blood bank purposes hardly justifies interference with a physiologic process.

HARRY BAKWIN, M.D.

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\*Haselhorst, G., and Allmeling, A.: *Ztschr. f. Geburtsh. u. Gynäk.* 98: 103, 1930.

†DeMarsh, O. B., Alt, H. L., Windle, W. F., and Hillis, D. S.: The Effect of Depriving the Infant of its Placental Blood, *J. A. M. A.* 116: 2568, 1941.



This important text *The Heart in Pregnancy and the Child-Bearing Age*<sup>3</sup> by Hamilton and Thomson may be regarded as a logical outcome of the Cardiac Clinic in the Boston Lying-In Hospital. This clinic established years ago has continuously expressed its experiences in current literature. Here the entire subject is gathered together and offered to the physician interested either in cardiology or in obstetrics.

The first section of the book opens with a general discussion of heart disease and continues with the treatment of the cardiac woman who becomes pregnant. Dr. Frederick C. Irving, Obstetric Chief of the Boston Lying-in Hospital, has written a section dealing with the delivery and obstetric aftercare of cardiac patients who have become pregnant. The new policy of this hospital regarding such patients, to subject fewer women to abdominal hysterotomy and to salvage more babies, has resulted in a lowering of the maternal mortality rate from 6.4 per cent to 2.6 per cent, and there has been but one death from heart failure compared to eight in the first series. Irving regards ether, carefully and properly given, to be the safest anesthetic in these cases, yet he does not feel that heart disease or failure per se contraindicates spinal anesthesia. Although in some reported series the majority of deaths of women with rheumatic disease who are pregnant occurred in the first twenty-four hours after delivery, the authors state "that congestive heart failure rarely occurs or re-appears following delivery at term." Circulatory burden is thoroughly discussed, many electrocardiographic tracings and x-rays of the heart are introduced to support the conclusions regarding the work of the heart during pregnancy.

The physiology of the normal and of the diseased heart in pregnancy are well contrasted. The authors regard the circulatory load in pregnancy to have reached the maximum before the ninth lunar month and note a decrease during the final weeks, tenth lunar month, of pregnancy. So far as the complications of pregnancy which are accompanied by renal or vascular lesions, generally grouped under term toxemias, are concerned, these abnormal manifestations are dealt with separately and at length. The authors do not regard eclampsia and pre-eclampsia as tending to be commonly followed by chronic heart disease, heart failure, or significant acute myocarditis. In discussing heart disease in young women, the authors state that the recurrence in rheumatic fever is very rare in the pregnant woman and in the puerperium, but may occur occasionally in girls under twenty-three years of age. There are chapters on neurocirculatory asthenia and bacterial endocarditis as well as other infrequently seen cardiac lesions in the childbearing age. The book is an outstanding contribution to obstetric literature.

PHILIP F. WILLIAMS.

In 1932 and 1935 Bernhard Zondek, in a monograph *Hormone des Ovariums und des Hypophysenvorderlappens*, reported his voluminous and fundamental researches dealing with the sex hormones. The present monograph<sup>4</sup> covers his work accomplished since then and including 1940, mainly carried out in Jerusalem.

The wide activities of this investigator and clinician embrace all of the sex hormones: pituitary, androgens, and estrogens as well as some of the other endocrine glands, both from an experimental and clinical standpoint.

The subjects covered include the occurrence of some estrogenic substances in nature; experimental and clinical investigations on the percutaneous use of estrogens and androgens; the effect of protracted treatment with high doses of estrogen; the fate of the sex hormones in the organisms; clinical investigations of the cycle of the female organism, and the mechanism of menstruation. Of particular interest is the inhibition of the pituitary function by estrogens which has been analyzed, inclusive of the gonadotropic, thyrotropic and parathyrotropic, and adrenotropic

<sup>3</sup>*The Heart in Pregnancy and the Childbearing Age.* By Burton E. Hamilton, M.D., Cardiologist to the Boston Lying-in Hospital, and K. Jefferson Thomson, M.D., Associate Physician, Metropolitan Life Insurance Company Sanatorium, etc. With a section: Delivery and Obstetrical After-Care of Cardiacs, by Frederick C. Irving, Professor of Obstetrics, Harvard Medical School, etc. 402 pages. Little, Brown and Company, Boston, 1941.

<sup>4</sup>*Clinical and Experimental Investigations of the Genital Functions and Their Hormonal Regulations.* By Bernhard Zondek. 264 pages. The Williams & Wilkins Company, Baltimore, 1941.

# Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

## Review of New Books\*

### Gynecology and Obstetrics

A second edition of Martius' *Gynecological Operations*<sup>1</sup> has appeared after an interval of four years. The first edition was most favorably commented upon in these reviews. Likewise the comment on the English translation, prepared by Dorland, was favorable.

The new edition contains several additional operations: The extended vaginal hysterectomy after Schauta-Stoeckel, as practiced in Vienna, is very clearly and simply depicted and described. Partial colpoclysis, according to Labhardt, by reduction of the vaginal canal to pencil diameter and building up of a perineum almost to the urethra, applied to old women who are poor operative risks, under local anesthesia, is described. Cottes' presacral sympathectomy has also been added. In addition to the new illustrations which illuminate the newly described operations, additional anatomical drawings of the female pelvic organs have been added. As mentioned in reviewing the first edition, the illustrations are particularly praiseworthy because of their simplification and schematization without loss of clearness and merit. The brief but incisive text is admirable in its clarity. This book has a wide scope.

ROBERT T. FRANK.

In this concise presentation *Essentials of Gynecology*<sup>2</sup> Brady and Kurtz have augmented a series of lectures on gynecology to nurses and have added a considerable amount of nursing procedures. Such a clear and concise presentation should form an excellent textbook not only for nurses and the preclinical medical student as well as a means of quick review for physicians preparing for hospital or State Board examinations. The division of the material is excellent, and the illustrations borrowed from many standard texts have been well chosen to correlate the descriptive text. There is a very fine chapter on female urology. The authors state that the interposition operation is preferred for complete prolapse of the uterus at both teaching institutions in Baltimore.

PHILIP F. WILLIAMS.

\*NOTE: The Department of Book Reviews will appear, in future, at regular intervals, namely in January, May, and September.

The present offering contains few items because a large number of reviews appeared recently. Books for review should be forwarded to Dr. Hugo Ehrenfest, 3720 Washington Blvd., St. Louis, Mo., at least two months in advance of the above dates.

R. T. F.

<sup>1</sup>*Die Gynaekologischen Operationen.* Von Professor Dr. Heinrich Martius, Direktor der Universitäts-Frauenklinik in Goettingen. Zweite verbesserte Auflage, 424 Seiten, mit 427, zum groessten Teil farbigen Abbildungen und Bilderreihen von Kaethe Droyssen, Verlag von Georg Thieme, Leipzig, 1911.

<sup>2</sup>*Essentials of Gynecology.* By Leo Brady, Assistant Professor of Gynecology, University of Maryland, etc., and Ethna Louise Kurtz, R.N., Head Nurse, Brady Urologic Institute, Johns Hopkins Hospital, etc. 57 illustrations, 251 pages. The Macmillan Co., New York, 1911.

The third volume of *The Therapeutics of Internal Diseases*<sup>8</sup> edited by George Blumer, is devoted to the infectious diseases as well as the various types of parasitisms. The book also takes up dehydration, edema, acidosis, metabolism, and the endocrine organs. While the first few sections are of little interest to the obstetrician, we find Martland giving a good discussion of asphyxia which should be of interest to the obstetrician.

The discussion of edema and dehydration is pertinent to the care of pregnant women, and the treatment of various toxemic conditions. McIvor in a well-written chapter on Pre- and Post-Operative Treatment has outlined the preparation for operation of patients with special diseases, all of which are common in gynecologic practice.

Under the section on Heart Diseases and Heart Failure there are two excellent sections on the heart in anesthesia and the general subject of marriage and pregnancy.

PHILIP F. WILLIAMS.

Cleckley in *The Mask of Sanity*<sup>9</sup> has selected those psychopathic personalities who do not fit into the community, and yet today, in the eyes of the law, are pronounced sane. They are serious problems for their relatives, the police, juries, and courts because in law, they are held responsible for their conduct. The author has seen a large number in the veteran hospitals. In these hospitals they form a serious problem as they cannot draw compensation.

These patients have no delusions, hallucinations, or signs of psychosis or psychoneurosis. They may commit crimes, such as forgery and bigamy, for which they are arrested. They take part in brawls, drunkenness, wife beating, and similar less serious disturbances. In spite of promises, they relapse again and again. Some, who show no real criminal tendencies, take drugs. To avoid the consequences of their misdeeds, they voluntarily seek hospitals as a temporary refuge and as an expedient to escape legal consequences. They soon weary of their confinement and insist upon being released. The hospital authorities are helpless because they cannot legally commit them, because of their being sane in the eyes of the law. Therefore they are again set at liberty. Among these individuals one finds business men, lawyers, physicians; among the nine case histories that he gives in detail, the author describes a well-known but unidentified psychiatrist. In this well and interestingly written monograph, the author pleads that some provision be made in law and in medicine to study and give adequate control and care for these patients.

ROBERT T. FRANK.

Gesell<sup>10</sup> has attempted the difficult task of reconstructing the life of Kamala, the wolf girl, from the diary placed at his disposal by the Reverend J. A. L. Singh in whose orphanage Kamala spent the nine years of her human association. She lived approximately eight years with her wolf foster mother and died at the age of seventeen years at the orphanage. It took fully two years to wean her from her wolfine ways. She never attained complete adjustment. The other child, Amala, lived for even a shorter period among humankind.

Dr. Gesell's interpretations are ingenious and interesting but far from convincing. This applies particularly to his attempted visualization of Kamala's wolf life which, to me, resembles a weak and emasculate imitation of Mowgli in Kipling's

<sup>8</sup>*The Therapeutics of Internal Diseases*. Volume III. Supervising Editor George Blumer, Clinical Professor of Medicine, Yale University School of Medicine, etc., and Associate Editor Albert J. Sullivan, Adjunct Clinical Professor of Medicine, George Washington and Georgetown Medical Schools, etc. D. Appleton-Century Company, Inc., New York, 1941.

<sup>9</sup>*The Mask of Sanity*. By Hervey Cleckley, Professor of Neuropsychiatry, University of Georgia School of Medicine. The C. V. Mosby Company, St. Louis, 1941.

<sup>10</sup>*Wolf Child and Human Child*, being a narrative interpretation of the life history of Kamala, the wolf girl. By Arnold Gesell, M.D., Director of Yale University Clinic of Child Development. Illustrated with photographs and drawings, 107 pages. Harper and Brothers, New York, 1941.

hormones. The estrogens do not react alike on these various functions. Of great importance are the investigations dealing with the production of uterine hemorrhage in animals below the primates, by means of gonadal and estrogenic hormones.

ROBERT T. FRANK.

This short brochure, *Female Sex Hormones*,<sup>5</sup> contains four articles on the sex hormones, presented at the Bicentennial of the University of Pennsylvania. The first, by Doisy, gives a clear description of the chemistry and physiology of "The Ovarian Follicular Hormone." Philip E. Smith presents the "Gonadotropic Hormones" and offers the evidence for and against there being two such hormones, one follicle stimulating and the other luteinizing.

R. T. Frank takes up the "Hormonal Blood and Urine Status," estrogenic, androgenic, progestational and gonadotropic, in the various conditions of health and disease. Elmer L. Sevringhaus concludes with a description of the "Sex Hormone Therapy in the Female."

ROBERT T. FRANK.

*Spermatozoa and Sterility*,<sup>6</sup> a clinical manual by Weisman, is addressed to gynecologists and urologists as well as general practitioners. It covers every aspect of the subject, even such an unnecessary one as a description of pregnancy tests. The anatomy, the physiology, and the chemistry of the spermatozoa are taken up. Minute techniques necessary for the study of sperma in the male and recovery in the female are described. The causes and the treatment of male sterility, the sperma in cryptorchidism, artificial impregnation and its legal aspects, are some of the subjects covered.

As every aspect of sperma and its implications are contained within the covers of this monograph, it is a valuable source book. The text is clear, concise, and well documented.

ROBERT T. FRANK.

### Miscellaneous

Gilbert Applehof, Jr., offers a valuable contribution to the study of the total structure of marriage,<sup>7</sup> namely the viewpoint of the minister. Rev. Applehof has been counseling couples on marriage for a great many years, both in the marriage clinic and in the rectory. The material in his book proceeds chronologically from adolescence, through the wedding and honeymoon, to the problems which arise later in marriage. He offers an interesting pre-marital questionnaire to be filled out by both partners which includes actual biographical data and attitudes toward such things as: finances, emotional adjustment, attitudes toward home and marriage, religious and sex instruction and attitudes, health, social adjustment, and understanding of marriage problems. Although the questionnaire is limited, it should give the counselor a good idea of the situation. Despite the many merits of this book, which is filled with universally important information, it is a marriage manual for the naive and religious couple, and in this capacity a truly excellent and inspiring guide, but the more sophisticated group, while learning a great deal, might not be willing to accept the continual combination of complete frankness and openness mingled with the stress on the religious aspect of the subject. Rev. Applehof portrays the sexual aspects of marriage without reserve, and yet on the next page will remind you that marriages are made in heaven.

YVONNE DEP. FRANK.

<sup>5</sup>*Female Sex Hormones*. By Edward A. Doisy, Philip E. Smith, Robert T. Frank, and Elmer L. Sevringhaus. 58 pages. University of Pennsylvania Press, Philadelphia, 1941.

<sup>6</sup>*Spermatozoa and Sterility*. By Abner I. Weisman, M.D., Adjunct Gynecologist, Jewish Memorial Hospital, N. Y., etc. With a Foreword by Robert L. Dickinson. 314 pages, 77 illustrations. Paul B. Hoeber, Inc., New York, 1941.

<sup>7</sup>*You Can Be Happily Married*. By Gilbert Applehof, Jr., Rector of St. John's Church, Alma, Mich. 218 pages. The Macmillan Company, New York, 1941.

# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Menstruation

Ashley-Montagu, M. F.: Physiology and the Origins of the Menstrual Prohibitions, *Quart. Rev. Biol.* 15: 211, 1940.

In a very concise article Ashley-Montagu here repeats the effort, often made before, to find in the results of recent scientific investigations a basis for an acceptable explanation of the old and still widely persisting belief that "the female during her catamenia is considered to be herself unclean and as noxious as the effluvium itself."

Folkloristic and related aspects of this question are quoted from the well-known works of Briffault, Havelock Ellis, Frazer, Ploss and others. Next are given brief quotations from a very large number of recent studies, experimental, psychologic and particularly chemie, and their results are critically analyzed. The thoroughness of the writer's efforts are proved, e.g., by his discovery that many beauticians now advise against a permanent hair wave during the period, because it will not take as well. He feels that there might be a modicum of truth in this assertion because "it is well known that the bioelectrical potential of the body differs from the normal during menstruation, as recently shown by Burr and Musselman." In this connection, however, he overlooks the fact that this momentary change in the electrical potential occurs only at the moment of rupture of the ripe follicle, i.e., some time before the start of the flow. It also seems surprising that the writer fails to mention the established and significant role played by menstrual blood in the causation of definite allergic phenomena.

In summarizing his studies, the author states that menstruous women apparently are capable of exerting noxious effects upon living tissues and that the responsible agent seems to be an alkylamine, probably thimethylamine. He concludes that it still is impossible to establish the possible physiologic origin of the various menstrual prohibitions.

HUGO EHRENFEST.

Cafizares, R.: The Utero-Ovarian Cycle in the Cuban Woman, *Rev. cubana de obst. y ginec.* 2: 105, 1940.

In a study of 200 white, negro, and mestizo women, the author developed several statistical conclusions which are interesting in comparison with common findings in the climate of the United States. The menarche varied between the ages of 12 and 15. Most white women had their menstrual onset at 14 years, the negro at 12, and the mestizoes showed two distinct groups commencing at the ages of 12 and 15.

In the group as a whole a normal menarche was reported for 58 per cent; dysmenorrhea in 31 per cent. A marked regularity in menstruation was noted: the negro most regular; white women second. The most common menstrual formula was three days every twenty-eight days. The age of menopause in this group was 45 to 54 years and the incidence of sterility was only 6.8 per cent.

R. J. WEISSMAN.

*Jungle Book*. More successful is the analysis of her life in the orphanage from which a number of important physiologic observations have been gleaned. Numerous photographs taken by Dr. Singh add interest to this unique biography.

ROBERT T. FRANK.

Griffith and Mitchell have revised their book on *Disease of Infants and Children* with a new title *Textbook of Pediatrics*.<sup>11</sup> The influence of the entire pediatric group is reflected in the long list of names of those who have contributed to or assisted in the preparation of the book. The text brings in line the most recent advances and modern ideas in the treatment of the diseases of children. The authors have been particularly generous in the development of those conditions in which the obstetrician would be interested either directly at the time of delivery or in the immediately postnatal period. They have devoted some forty pages to the disease of the newborn infant, not only from the standpoint of prematurity and immaturity but as well from the standpoint of infections and general conditions. The chapter on breast feeding and artificial feeding in the first year of life discusses the nutritional problems the obstetrician who continues care of the child will have to handle. One feels that this should be an excellent volume to have at hand in the Maternity Division of any hospital.

PHILIP F. WILLIAMS.

Dr. Mary McKibbin-Harper in the new book *The Doctor Takes a Holiday*<sup>12</sup> has brought together some interesting sketches of her travels in the Far East. Already well known for her previous travel books, Dr. McKibbin-Harper lays before one not only the tourist sights of the Near East and Orient but carries one through the various phases of medical practice in those lands. This unusual combination of travel lore, sociology, and medicine in foreign parts makes the book one which once begun is not easily laid down.

PHILIP F. WILLIAMS.

<sup>11</sup>Textbook of Pediatrics. By J. P. Crozer Griffith, Emeritus Professor of Pediatrics in the University of Pennsylvania, etc., and A. Graeme Mitchell, Professor of Pediatrics, College of Medicine, University of Cincinnati, etc. Third edition, revised and reset, 220 illustrations, 991 pages. W. B. Saunders Company, Philadelphia, 1941.

<sup>12</sup>The Doctor Takes a Holiday. By Mary McKibbin-Harper, M.D. Illustrated, 349 pages. The Torch Press, Cedar Rapids, Iowa, 1941.

The third purpose is to determine the date of the following menstrual flow in women who have irregular cycles. This knowledge will eliminate the necessity for performing repeated biopsies of the endometrium to obtain a premenstrual endometrium.

J. P. GREENHILL.

**Vollmann-Siebr, U.:** Investigation of the Body Temperature of Women in Correlation With the Phases of the Genital Cycle, *Monatsschr. f. Geburtsh. u. Gynäk.* 111: 41 and 121, 1940.

The author recorded the daily rectal temperatures for 284 menstrual cycles in 37 women and found that there is a biphasic wave-like curve during each menstrual cycle. There is a decrease in temperature following the menses and a characteristic increase in the intermenstruum. Likewise, there is a rise in temperature in the premenstrual period and a sudden fall just before the onset of bleeding. Men, children, and women past the menopause do not show any cyclic fluctuations in the rectal morning temperature. During pregnancy the temperature is strikingly constant. During the amenorrhea associated with lactation, there are also no cyclic variations but just before the onset of the first menses after delivery, the temperature exhibits the biphasic curve again.

The author made use of the temperature curves to determine the length of the post- and premenstrual phases. He observed that the duration of the premenstrual phase is relatively independent of the menstrual cycle, whereas the postmenstrual phase varies directly with the length of the cycle.

J. P. GREENHILL.

**Vollmann, R.:** Statistical Analysis of the Phases of the Genital Cycle in Women by Using Intermenstrual Pain as the Criterion of Ovulation, *Monatsschr. f. Geburtsh. u. Gynäk.* 110: 137, 1940.

The symptomatology, etiology, and physiology of intermenstrual pain are discussed by Vollmann based on experimental research and a menstrual calendar record kept for three years by a patient. The author's hypothesis is that intermenstrual pain is similar to a viscerosensory reflex, the result of tubal spasms, determined by the menstrual cycle. In the opinion of the author, intermenstrual pain coincides with ovulation.

J. P. GREENHILL.

**Croci, C.:** The Cold Pressor Test During the Menstrual Cycle, *Monatsschr. f. Geburtsh. u. Gynäk.* 110: 334, 1940.

The author performed the cold pressor test on 18 women during various times in the menstrual cycle. In 14 cases he found a diminished response of the blood vessels at the time which corresponded to ovulation. He believes that the change in the reaction was an indication of impending ovulation.

J. P. GREENHILL.

**Morton, Daniel G., and Hayden, Charles T.:** Incidence of Ovulation as Determined by Endometrial Biopsy, *West. J. Surg.* 49: 15, 1941.

The investigation of the endometrium in successive cycles in normally menstruating, healthy young women indicates that anovulatory cycles are rare, probably not more than one in ten up to the age of 40 years. With the approach of menopause, after 40, the incidence of anovulatory cycles increases markedly, about one in two. Thus, it appears that the presence of essentially regular menstruation can be interpreted almost uniformly as an incidence of normal, regular ovulation in women below 40.

These observations tend to minimize the importance of endometrial biopsy in sterility investigations in normally menstruating women.

HUGO EHRENFEST.

Neufeld, N., and Boas, v. Emde: **A Critical Review of the Cycloscope Method for the Diagnosis of Ovulation**, *J. Contraception* 4: 99, 1939.

During the last few years, Samuels of Amsterdam has published a number of articles in different medical journals describing a new method for the determination of the time of ovulation. Samuels makes the assumption that the cellular gas metabolism in the tissues, or tissue respiration, is a measure of the hormonal processes in the human body, and he describes a simple instrument, which he calls the cycloscope, by means of which the reduction time of the oxyhemoglobin in the blood can be exactly measured.

Samuels thinks that by his reduction figures he has gained an insight into the hormonal processes which take place in the body of healthy and ill men and women, and he applies the spectroscopy method extensively for diagnostic and therapeutic purposes. He thinks that after a short "provocative" treatment of the endocrine glands with short waves, he can diagnose all kinds of endocrine troubles and even state which of the glands is hyper- or hypofunctional. The diagnosis of tumors, the differential diagnosis of malignant and benign growths, of every early pregnancy, of impending abortion, etc., all this is a simple matter with this omnipotent instrument.

The spectroreductometer appears to be the same as the instrument of Drs. Dausset and Ferriers. The cycloscope is the same instrument as the French one, only somewhat simplified.

The instrument with which Norbert Neufeld and van Emde Boas made their tests was a spectroreductometer which is sold as Dr. Samuels' cycloscope.

As the authors have now judged the instrument to be faulty and the method to give no results to prove that there is repeated ovulation, they state that even if, with another instrument and another method, they could obtain a curve of the reduction time, it would be rash to draw conclusions that the reduction time is related to ovulation.

Dr. Samuels' proofs that ovulation takes place twice or three times a month are not conclusive. His foremost proofs are first, the results of the cycloscope, which the authors reject; and second, the published findings of laparotomies, which are very few and unconvincing. Various authors have often emphasized the fact that from inspection alone it is impossible to state with certainty how ripe the follicles are, or how old the corpus luteum is.

J. P. GREENHILL.

Palmer, R., and Devillers, J.: **Ovarian Cycle and Temperature Curve. Utilization for the Diagnosis of the Date of Ovulation**, *Comp. rend. Soc. franç. de gynéc.* 9: 60, 1939.

During the past year the authors have analyzed the temperature curves of women in whom the menstrual cycle was being studied. Rubinstein had shown that rectal temperatures taken between six and seven in the morning are at their minimum on the day of ovulation. Palmer and Devillers were also struck with the low temperatures observed at the beginning of the luteal phase of the cycle. They believe that whereas it is not permissible to maintain that one can predict the day of ovulation and the formation of a corpus luteum from the temperature curve, nevertheless when other signs and symptoms of ovulation are present, the temperature curve fixes the date of ovulation in a more precise manner than do the other signs. This information is important for three purposes. First to determine the period of fecundation. The beginning of this period is at the time of the second lowest temperature, the most favorable time is at the lowest temperature, and the entire period continues only forty-eight hours after the drop in temperature.

The second purpose is to be able to attribute to ovulation certain intermenstrual disturbances such as pain, bleeding, leucorrhea, breast symptoms, and general and psychic disturbances.



had failed, a splenectomy was performed. Normal periods were present during the year following operation. Careful examination of the blood including platelet counts and estimates of bleeding time are emphasized in the investigation of menorrhagia where no local cause is found.

CARL P. HUBER.

**Greenhill, J. P., and Freed, S. C.: The Mechanism and Treatment of Premenstrual Distress With Ammonium Chloride, *Endocrinology* 26: 529, 1940.**

It is postulated that the symptoms which occur in many women, premenstrually, result from the increase in extracellular fluid following sodium ion retention in the various tissues of the body. Therapy with ammonium chloride for the purpose of removing the extracellular fluid thus formed, is effective in relieving the premenstrual distress or tension.

The treatment was uniformly successful. All the patients were definitely relieved and were highly gratified with the therapy. Gross edema did not occur in the patients who had previously demonstrated it. Distention of the abdomen, nausea, and migraine were absent or insignificant during the ammonium chloride therapy. The patients claimed that they were less irritable and not subject to the periodic emotional upsets. All patients stated that there was an improved sense of well-being.

J. THORNWELL WITHERSPOON.

**Miller, Norman F.: Dysmenorrhea, *Canad. M. A. J.* 42: 349, 1940.**

The best approach to the treatment of dysmenorrhea is through an understanding of the fundamental anatomy and physiology of the structures involved. The nerve supply to the uterus may be of importance, due to the relation between emotional disturbances and menstrual disorders and also because of pathologic changes present in the nerve fibers and ganglion cells themselves. Disturbances in the blood supply of the pelvic organs, particularly stasis, may play an important part in the causation of congestive dysmenorrhea. Endocrine imbalance which may be either insufficient corpus luteum hormone or decreased estrogenic stimulation is important. The author warns that malpositions of the uterus, fibroids, infections, and endometriosis may cause dysmenorrhea but more often they do not. He feels that surgical treatment of dysmenorrhea is seldom necessary and that presacral neurectomy should be a last resort.

Successful management depends upon a willingness to meet the challenge of dysmenorrhea as a medical problem, a good understanding of the subject, recognition that there may be overlapping of predisposing and causative factors. Treatment should have two objectives: (1) relief of pain and (2) the correction of the underlying cause.

CARL P. HUBER.

**Wittkower, E., and Wilson, A. T. M.: Dysmenorrhoea and Sterility. *Personality Studies, Brit. M. J.* 2: 586, 1940.**

From a survey of biographic studies on 87 patients with dysmenorrhea, sterility, or both, the author points out that these complaints usually are secondary to certain psychologic characteristics in the individual, which antedate the appearance of the symptoms.

The survey included 57 unselected patients with primary dysmenorrhea and 30 patients with sterility of some years' duration. Of these, 19 complained of both dysmenorrhea and sterility. The control group consisted of 30 primigravidas who had never had dysmenorrhea.

In considering the childhood characteristics, the reaction to the various phases of adolescence, and the adult personality of these individuals, the author found certain personality types predominantly associated with each of the complaints under consideration. There was noted an overlapping of these personality types in individuals complaining of both dysmenorrhea and sterility.

Netter, Albert: Anovulatory Menstruations, *Presse méd.* 48: 333, 1940.

The author reviews the known animal and human experimental endocrine facts relative to spontaneous and induced anovulatory menstruation. He concludes that the normal woman can have anovulatory menstrual periods from puberty to menopause. During the mature sexual period, the failure of ovulation is exceptional. Such a failure of ovulation does account for certain cases of sterility with or without functional bleeding. The treatment of these latter cases unfortunately is still very deceptive.

CLAIR E. FOLSOME.

Soskin, Samuel, Wachtel, Hans, and Hechter, Oscar: Prostigmine Methylsulfate for Delayed Menstruation, *J. A. M. A.* 114: 2090, 1940.

The authors feel that since there is evidence in favor of the fact that the specific proliferative effects of estrogen are due to the acetylcholine liberating properties of the hormone, there is some connection between the parasympathetic nervous system and menstrual phenomena. It is seemingly possible that cases of delayed menstruation now generally ascribed to temporary endocrine dysfunctions might occur despite normal hormone secretion and be due to abnormally decreased vascular responsiveness. An attempt was, therefore, made to treat these cases by pharmacologic rather than by endocrine means.

The preparation used was prostigmine methylsulfate (1-2,000), and this substance invariably precipitated the menstrual flow in cases of menstrual delay (nonpregnant). The average time that elapsed between the last injection and the beginning of the flow was twenty-eight hours. The longest interval was seventy-eight hours, and the shortest interval was four hours. One to three injections were given on successive mornings, and the amount given was usually 2 c.c. The prostigmine had no effect on cases of delayed menstruation due to pregnancy. This latter group of cases were all given 2 c.c. on three successive mornings. A suggestion is made that this test could be used as a test for pregnancy.

WILLIAM BERMAN.

Shute, E.: The Diagnosis and Treatment of the Common Disorders of Menstruation, *J. Canad. M. A.* 40: 38, 1939.

Shute emphasizes the importance of attempting to determine the endocrine disturbance associated with menstrual abnormalities before hormone therapy is instituted. He recommends as a practical procedure, the estimation of blood estrogenic hormone level from determination of its antiproteolytic power.

Endocrine menorrhagia is usually associated with excessive blood estrogen. Oligomenorrhea is usually due to the reverse. Amenorrhea may be associated with either high or low blood levels. It is essential to determine which state is present and to discover if cyclic variations are present. The amenorrhea at the menopause may show similar relationships.

Dysmenorrhea also may be associated with low blood estrogen levels as well as with excessive estrogenic secretion.

All of these conditions must be looked upon as symptoms and not as syndromes. They should never be treated empirically. Where low estrogenic values are present, substitution therapy with estradiol intramuscularly is recommended. In the presence of excessive estrogenic activity, the following antiestrogens are suggested arranged approximately in order of ascending price and effectiveness: thyroid extract, prolan preparations, wheat germ oil, progesterone.

CARL P. HUBER.

Snaith, Linton: Menorrhagia Due to Essential Thrombocytopenia, *Lancet* 2: 684, 1940.

The author reports the case of a woman 27 years old with severe menorrhagia of two and one-half years' duration. No local or hormonal cause for the bleeding was determined and thrombocytopenia was discovered. After conservative measures

were given after the fourth spinal puncture. It had been found that corpus luteum extract given orally once during an earlier attack had given partial relief.

Following hypodermic use of proluton in the midcycle, the patient ceased to have headaches, vomiting, and photophobia.

The authors make no comment upon the case other than to review the facts.

CLAIR E. FOLSOME.

**MacGregor, T. N.: Amenorrhoea: Its Aetiology and Treatment, Brit. M. J. 1: 717, 1938.**

With the premise that disappointing response to treatment of amenorrhea with the endocrines is probably due to indiscriminate administration, 97 cases are presented which have been investigated as thoroughly as present-day methods permit. The importance of a complete history and the role of anorexia nervosa and psychic shock in the production of amenorrhea is brought out. X-ray of the sella turcica, basal metabolic rate, determination of sugar tolerance, and determination of the amount of gonadotropic and follicular hormone excreted in the urine serve as guides toward a more rational hormonal treatment.

Twenty out of 97 cases investigated showed the amenorrhea to be due to recognizable pathology in the pituitary, ovaries, or uterus and in a few cases to systemic disease. In 77 cases, although no obvious pathologic condition was observed, laboratory findings disclosed a disturbance of function, particularly in the ductless glands and concerned with the menstrual process. These cases are described as "functional."

In treatment of functional amenorrhea, anorexia nervosa was most difficult and was treated with combined systemic and psychologic methods, followed by gonadotropic hormone. Patients with low basal metabolic rates were given thyroid and those with obesity were treated by a strict antiobesity diet.

Thirty patients showing excess gonadotropic hormone in the urine were treated with estrogenic substances (estradiol benzoate). Twelve of them failed to respond to treatment. Sixteen responded irregularly. In 2 patients the menses became regular, and in one, remained regular for twelve months.

Three out of 4 patients treated with anterior pituitary gland extract showed no response, while in the fourth uterine bleeding was produced for five months. Of 16 patients treated with urine gonadotropic hormone only two responded satisfactorily. Thirty patients were treated with serum and urine gonadotropic hormone, with 10 responding satisfactorily.

It is concluded that although the estrogens are of value in a few cases of amenorrhea in many they are contraindicated, since they produce a further inhibition of an already underfunctioning hypophysis. The most useful preparation in treatment of those cases due to hypopituitary secretion seems to be serum gonadotropic hormone alone or combined with the urine gonadotropic hormone.

F. L. ADAIR AND T. G. GREADY.

**Lövset, J.: Follicular Persistence, a Constitutional Malady With (Incomplete?) Dominant Inheritance, Monatschr. f. Geburtsh. u. Gynäk. 111: 154, 1940.**

The clinical picture of follicular persistence is described by Lövset as a condition where periods of amenorrhea alternate with periods of metrorrhagia. In most instances, there is relative or absolute sterility. No satisfactory explanation has been found to account for this condition. The author reports a series of 10 families, from each of which 1 or 2 patients had come for treatment of the disturbance. The author's series also includes 2 pairs of identical twins in whom the disease appeared at the same time, ran the same course, and in whom the findings in uterus and ovaries at operation were identical. In 7 families there was evidence of cases of follicular persistence among relatives on both the father's and mother's sides. Because of this, the author feels it is justifiable to assume the presence of a dominant hereditary factor.

J. P. GREENHILL.

The author found that although the incidence and intensity of psychologic maladjustment in some adults is to some extent the result of their disorders, the majority of ailing patients show definite maladjustment from early childhood.

In conclusion, he suggests probable explanations for individuals of certain personality types developing complaints typical of that type.

FRED L. ADAIR AND W. H. PHILLIPS.

Geller, Fr. Chr.: Infection and the Menstrual Cycle, München. med. Wehnschr. 87: 1110, 1940.

Geller discusses the relationship of infections and the menstrual cycle stating that the onset of various infectious diseases, such as scarlet fever, diphtheria, angina, furunculosis, etc., is strikingly frequent during the premenstrual period and during the first days of the menstrual cycle and that if infectious disease is already present, very frequently, there are further elevations of temperature during these periods. This fact has been recognized in tuberculosis.

In latent focal infections (granuloma of teeth, follicular tonsillitis, etc.), premenstrual elevations of temperature also occur so that fever in the premenstrual period almost always indicates a focal infection somewhere in the body. The premenstrual phase (corpus luteum) causes an increased susceptibility to infection. This phenomenon can be explained only by a decrease of the nonspecific resistance of the human serum to bacteria. Immunobiologic examinations confirm the fact that premenstrual elevation of temperature during infection is most probably due to increased bacterial activity, resulting from lowered bactericidal properties of the serum. This rise in temperature may, of course, be due partly to increased absorption of bacterial toxins and cellular debris, caused by better blood supply during this period.

C. E. PROSHEK.

Le Doux, L. A.: Some Observations on the Influence of Toxemias Upon Menstruation, New Orleans M. & S. J. 91: 463, 1939.

Toxemias associated with acute infectious diseases affect menstruation adversely. The untoward effect will depend upon the severity as well as the duration of the infectious process. Suppurative infections appear to furnish the greatest percentage of ovarian impairment. Toxins appear to have a stimulative as well as a depressive effect upon the ovaries, depending in which phase of the cycle they become active. The harmful effects of toxins may be upon the circulating hormone, the follicle, or both.

With the possible exception of gonorrheal infection, these disturbances are functional and capable of correction. Not more than one or two months should elapse before instituting treatment. Only such patients as have been subjected to a severe or long-standing toxemia may become permanently disabled. These patients should not be left entirely to their own devices or to nature, but should be treated as promptly as possible. In considering therapy, the author emphasizes that the use of ovarian hormones plays only a part in it.

J. P. GREENHILL.

Mach, Rene S., and Meyrat, Gilbert: Recurrent Hemorrhagic Meningismus Following Ovulation Period, Presse méd. 48: 292, 1940.

The authors report an interesting case of recurrent hemorrhagic meningismus following ovulation in a woman 31 years old. The patient gave a history of menarche at age of 17; irregular menses associated with migrainelike headaches, and moderate leucorrhoeal flow fifteen days before advent of her periods. A pregnancy at the age of 26 years temporarily removed these symptoms.

The patient was brought to the hospital with a typical syndrome of meningismus during her intermenstrual period. There were positive Kernig and Trousseau signs. Lumbar puncture revealed blood-tinged spinal fluid. In all, four lumbar punctures were done and findings similar to the first were recorded. Three ampoules of proluton

The cardiac accidents do not appear to be induced by the climacteric mechanical difficulties in the circulation balance. Neither the arterial or venous blood pressures nor the blood volume are sufficiently increased to make them explanatory of the menopausal asystoles.

The cardiac accidents of the menopause appear to be essentially based upon the neurovegetative imbalance and the cardiac and vasomotor disturbances which accompany the climactericum.

The prognosis of the menopausal cardiac accidents is very poor. The association of cardiac and endocrine therapy seems of but little value. Nevertheless this question of combining the treatments warrants more studies.

The endocrine therapy would probably be more favorable were it used prior to the cardiac decompensation period. Treatment of the cardiac accident of the menopause should be preventive.

CLAIR E. FOLSOME.

Hall, Francis C.: Menopause Arthralgia, *New England J. Med.* 219: 1015, 1938.

The thesis of a specific menopause arthritis is supported by many writers. From a thorough study of 71 patients, Hall concludes that in many of these patients there does not exist a true arthritis, and for this reason he prefers the term menopause arthralgia. In this latter group the joint pain is found associated with other symptoms ascribable to ovarian deficiency. There were 53 patients suffering from arthralgia. Of 40, adequately treated with estrogenic material, 80 per cent were materially relieved of the menopausal and joint symptoms.

HUGO EHRENFEST.

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## Correspondence

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### The Colostrum Skin Test for the Diagnosis of Pregnancy

*To the Editor:*

Drs. Falls, Freda and Cohen presented a paper entitled "A Skin Test for the Diagnosis of Pregnancy" in March, 1941, issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*. Their test involved the use of a solution of colostrum, and they intimated that this secretion might contain certain specific proteins or a protein-like substance which when injected intradermally would produce a difference in allergic response between pregnant and nonpregnant individuals.

The special solution of colostrum which they utilized was obtained and prepared under definitely standardized conditions. The technique of administering the intradermal injections was specific and outlined in detail. They interpreted the end reactions of the injections definitively, and considered the patient to be pregnant if only a slight reaction or no reaction ensued. Only when a marked allergic response manifested itself, did they consider the patient as nonpregnant. For details concerning their exact technique and procedure, one may refer to the original publication (*AM. J. OBST. & GYNEC.* 41: 431, 1941).

Falls, Freda, and Cohen presented the results of tests performed on 265 known pregnant women and 163 women who were definitely not pregnant nor post partum. They claimed that in the tests done on known pregnant women only "five false reactions" were obtained. Of the tests performed on the 163 nonpregnant women, it was stated that "typical nonpregnancy reactions were obtained in all but four patients, in whom typical pregnancy reactions were obtained which would have led to an incorrect diagnosis if the test alone had been relied upon."

From their results, it is evident that the authors were able to diagnose correctly pregnancy in 265 cases with an accuracy of 98.1 per cent. Of the 163 women who were not pregnant, they were able to say that 97.55 per cent of them were not pregnant. Owing to these excellent findings, Falls and his colleagues were quite sanguine regarding the diagnostic value of their test, and they therefore concluded their paper with the following remarks: "If our results are con-

Donald, H. R.: *The Female Climacteric and the Menopause*, Brit. M. J. 1: 727, 1938.

The importance of differentiation between the climacteric and menopause is discussed; the climacteric is a general female epoch characterized by certain changes in function which lack any uniformity and which show great variations in severity, while the menopause is merely a local disturbance or cessation of menses.

Cases are presented in which the menopause was accompanied by occasional mild phenomena as hot flushes while the onset of the wide assortment of nervous symptoms which characterize the climacteric was delayed for fifteen years or more.

The distinction between climacteric and menopause is emphasized to counteract the impression that indications for endocrine, particularly estrin therapy are limited to the short period which follows the cessation of menses.

F. L. ADAIR AND T. G. GREASY.

Rowlands, I. W., and Sharpey-Schafer, E. P.: *Effect of Oestradiol Benzoate on the Amount of Gonadotrophin Found in the Pituitary Gland and Urine of Postmenopausal Women*, Brit. M. J. 1: 205, 1940.

Five women in the postmenopausal period suffering from incurable diseases were given intramuscular estradiol benzoate for varying periods before death. The anterior pituitary glands were removed at autopsy and were dried and weighed. Their potency was tested by preparing an extract and injecting hypophysectomized rats. These were controlled by five similar but untreated women.

The estradiol benzoate administration did not change the weight of the pituitary glands, but did decrease the amount of gonadotrophic substance. Microscopic studies of the rat ovaries showed that both hormones of the gonadotrophic complex were equally depressed.

The authors feel that this experiment shows the inhibitory effect of estradiol benzoate on the gonadotrophic activity of the anterior pituitary. They admit, however, that it might be due to increased pituitary activity which empties the gland of its hormone.

FRED L. ADAIR AND GEORGE BOHLENDER.

O'Donovan, D. K.: *Stilboestrol in Menopausal Therapy*, Irish J. M. Sc. p. 159, April, 1940.

Stilboestrol (neo-oestranol 1) has an important role in menopausal therapy. It is effectively assimilated when given orally, and its reasonable price means that estrogenic treatment can be provided for hospital patients. In general, its mild toxic symptoms are not sufficient to outweigh the beneficial results obtained with it. Pending further experimental investigation, it is not considered advisable, nor is it usually necessary, to use it in any individual case for more than three months without interval. It is not considered a very successful therapy for the surgery menopause.

WILLIAM C. HENSKE.

Bloch-Michel, H., and Prin, A.: *Menopause and the Mitral Cardiopathies. The Cardiac Accidents of the Menopause*, Ann. d'endocrinol. 1: 257, 1939.

The authors have followed 8 cases of mitral lesions in each of whom the advent of menopause seemed to be more than just an incidental factor in cardiac decompensation. They contend that the menopause represents for women with mitral lesions a time fully as dangerous as that in puerperal stages. The cardiac accidents of the menopause are serious. They may appear in the premenopausal period or some months following the cessation of menses.

The cardiac accidents of the menopause are characterized by the frequent association of common asystoles, vasomotor findings (Raynaud's syndrome), hemiplegia, convulsive crises, etc.

P., and von Hamm, E.: *South. M. J.* 31: 169, 1938. Friedman, J. J., and Fink, H.: *AM. J. OBST. & GYN.* 36: 116, 1938. Parsons, S. R.: *Surg., Gynec. & Obst.* 68: 187, 1939. Hadley, H. G.: *AM. J. OBST. & GYN.* 39: 894, 1940. Mandy, T. E., and Mandy, A. J.: *AM. J. OBST. & GYN.* 41: 109, 1941).

In conclusion, it may be stated that we were unable to duplicate or confirm the excellent results obtained with this test by Falls, Freda, and Cohen. Our figures indicate a gross inaccuracy of over 29 per cent in 150 such tests. We agree with Falls and his colleagues in their statement, referring to the other skin tests for pregnancy, that owing to the high percentage of false reactions the use of these procedures for diagnostic purposes is useless.

However, since no one group of investigators can lay claim to being the "last word" in scientific research, we herewith have submitted our findings and look forward to the future reports on the subject.

ABNER I. WEISMAN, M.D.

ARNOLD F. SNYDER, M.D.

NEW YORK, N. Y.

The above letter was submitted to Dr. Falls for his comment. He states in his reply that the test under consideration has continued to give him good results and that favorable results on its employment have been reported by Dr. Raymond E. Watkins, of Portland, Ore., Dr. Russell W. Alles, of Detroit, Mich., Dr. William T. Pride, of Memphis, Tenn. (94 per cent correct), and Dr. Arthur Bill, of Cleveland, Ohio. Dr. Falls also states that at the Cook County Hospital, 30 out of 36 potential ectopic pregnancies have been diagnosed correctly by this method. He has had no other communications indicating a degree of failure such as that reported by the writers of the foregoing letter.

### Additional Report on a Case of Cerebellar Cyst Complicating Pregnancy

*To the Editor:*

In the September, 1937, issue of *THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, I reported a case of Angiomatosis Retinae (von Hippel's disease, Lindau's disease) Complicated by Pregnancy. This case was reported because of the extreme rarity of the condition. It appeared to be the second case recorded in the literature in which pregnancy was noted as a complication, and was the first for which cesarean section was performed with angiomatosis retinae as the sole indication.

Angiomatosis retinae is a disease characterized by immense dilatation and tortuosity of retinal vessels, and the development of angiomas usually toward the peripheral retina (von Hippel's disease). It is frequently associated with angiomatic cysts of the brain and spinal cord, and malformations or cysts of various somatic organs. When this association is present the condition is known as Lindau's disease.

As a result of ophthalmologic consultation with Dr. John N. Evans, cesarean section under local anesthesia was deemed advisable. It was felt that the already dilated and diseased vessels might not withstand the marked vascular strain that inevitably accompanies spontaneous labor. The fact that there might be an associated lesion elsewhere in the central nervous system or in one of the parenchymatous organs was also considered.

On April 9, 1936, a classical section was performed under local anesthesia, and the patient was delivered of a normal, living, male infant, weighing 2,940 Gm. Sterilization was recommended, but consent was refused by the husband. The postoperative course was uneventful and the patient was discharged from the hospital on April 26, 1936, seventeen days after the operation.

firmed by others it will make the diagnosis of early pregnancy much simpler, quicker and more economical than the methods we now have at our command."

The extreme simplicity of this method of testing and the excellent results obtained prompted us to attempt to corroborate their findings. Accordingly, colostrum was collected and prepared in exactly the manner advocated by these investigators. Their technique of injection and method of reading the reactions were closely followed.

Our series consisted of 150 women, of whom 100 were definitely pregnant and 50 definitely not pregnant. The 100 definitely known pregnant cases were white women from the obstetric out-patient department of the Metropolitan Hospital who were carefully selected so that they were between five and eight months pregnant. All these patients "felt life" and the fetal parts were palpable by abdominal examination in every case. The 50 nonpregnant women were nurses and patients from our hospitals who were regularly menstruating and who had no reason to believe that they were in a pregnant condition.

*Results.*—Of the 100 definitely known pregnant women, 48 per cent gave no allergic reaction whatsoever, 27 per cent gave evidence of some slight reaction, which we, according to the Falls' method, classed as "weak reactions," while 25 pregnant women gave strong full-blown allergic skin reactions from the intradermal colostrum solution. The "weak reactions," as suggested by Falls, were grouped together with the cases which did not react, and an analysis of the figures revealed that 75 per cent of the pregnant women reacted as Falls and his associates had predicted. However, there was an error of 25 per cent in these attempts to diagnose pregnancy correctly.

Of the 50 nonpregnant women who were regularly menstruating, 31 (62 per cent) gave strong allergic responses to the injections which was indicative, according to Falls and others, of the state of nonpregnancy. However, 13 women did not react at all to the injections and 6 reacted very slightly. This meant that 19 out of 50 cases gave false reactions which is an error of 38 per cent in attempting to diagnose the state of nonpregnancy by this test.

After having performed 150 colostrum intradermal tests for pregnancy with a percentage error of over 29 per cent, it was not considered feasible to continue with any further testing, in view of the relative inaccuracy of the test. Aside from the large error which we obtained when using the exact same technique employed by Falls, Freda, and Cohen, there are many other drawbacks in using an allergic skin reaction for pregnancy testing. The woman who is markedly allergic to any foreign protein, the interference from endocrine and metabolic dysfunctions, the necessity of a thorough knowledge of the fundamentals of wheal formation, the personal error in interpreting reactions and the variation in the chemical constituents of colostrum in different source individuals, all tend to make this allergic skin test of dubious value, at least for the present, as an aid in the diagnosis of pregnancy.

Perhaps with further study and standardization, this test can be made useful for the average practitioner, but until then, the profession should be cautioned against basing any diagnosis of pregnancy solely upon the use of the colostrum test for pregnancy. We feel that this test, because of the high degree of inaccuracy in the hands of those other than the original workers, may be placed in the same category as two earlier intradermal skin tests for pregnancy, the Gruskin test (*Am. J. Surg.* 31: 59, 1936) and the Gilfillen and Gregg intradermal test (*Am. J. Obst. & Gynec.* 32: 498, 1936). The former employed the use of a specially prepared placental protein substance, while the latter test involved the injection of antuitrin-S as a means of diagnosing pregnancy. Both of these intracutaneous skin tests for pregnancy were at first highly praised by their proposers, but neither could be considered of much value in view of further reports by other investigators (Weisman, A. I., and Yerbury, C. C.: *M. Rec.* 145: 203, 1937. Schwartz, E.: *Am. J. Surg.* 33: 225, 1936. Schneider, B., and Cohen, A.: *J. A. M. A.* 109: 115, 1937. Gill, A. M., and Howkins, J.: *Brit. M. J.* 2: 1069, 1937. Weisman, A. I.: *Am. J. Obst. & Gynec.* 35: 354, 1938. Gersh, I.: *Am. J. Obst. & Gynec.* 35: 301, 1938. Frank, C. W., and Wahrsinger, P. B.: *Am. J. Obst. & Gynec.* 35: 303, 1938. Lass, P. M., Enderle, E. S., and Kurzrok, R.: *Endocrinology* 23: 71, 1938. Hoffmann, P. E., and Fough, F. L.: *Am. J. Obst. & Gynec.* 35: 680, 1938. Graffagnino,



## Books Received

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**THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY.** By W. A. Newman Dorland, M.D., F.A.C.S. Nineteenth edition, revised and enlarged, with 914 illustrations, including 269 portraits. 1647 pages. W. B. Saunders Company, Philadelphia, 1941.

**GENITAL FUNCTIONS AND THEIR HORMONAL REGULATIONS.** Clinical and Experimental Investigations. By Bernhard Zondek. Illustrated, 264 pages. The Williams & Wilkins Company, Baltimore, 1941.

**COMMUNITY ORGANIZATION FOR HEALTH EDUCATION.** A Committee Report of the American Public Health Association. 120 pages. The Technology Press, Cambridge, Mass., 1941.

**ABDOMINAL SURGERY OF INFANCY AND CHILDHOOD.** By William E. Ladd, Professor of Child Surgery at Harvard Medical School, etc., and Robert E. Gross, Associate in Surgery, Harvard Medical School, etc. 268 illustrations, 455 pages. W. B. Saunders Company, Philadelphia, 1941.

**ENDOCRINOLOGY.** By R. G. Hoskins, Ph.D., M.D., Director of Research, the Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School. Illustrated, 388 pages. W. W. Norton & Company, New York, 1941.

**TUBERCULOSIS Y PSICOPATIAS.** By Dr. Ramon Melgar. 266 pages. Talleres Graficos "Gasperini," Buenos Aires.

**BIOLOGICAL SYMPOSIA.** Vol. III. Muscle. Edited by Wallace O. Fenn, Professor of Physiology, School of Medicine, University of Rochester, N. Y. Illustrated, 370 pages. The Jaques Cattell Press, Lancaster, Pa., 1941.

**RADIATION THERAPY.** Its Biologic Fundamentals. By Friedrich Ellinger, M.D., Research Fellow, Radiotherapy Department, Montefiore Hospital, New York City. 79 figures in text, 360 pages. Nordemann Publishing Company, Inc., New York, 1941.

**OBSTETRICS FOR NURSES.** By Joseph B. DeLee, M.D., Professor of Obstetrics and Gynecology, Emeritus, University of Chicago, etc., and Mabel C. Carmon, R.N., Chief Supervisor and Instructor in the Birth Rooms, Chicago Lying-In Hospital, etc. Twelfth edition, revised. 291 figures, 651 pages. W. B. Saunders Company, Philadelphia, 1941.

**THE PREMATURE INFANT.** Its Medical and Nursing Care. By Julius H. Hess, M.D., Professor and Head of Department of Pediatrics, University of Illinois College of Medicine, etc., and Evelyn C. Lundeen, R.N., Supervisor, Premature Infant Station, Sarah Morris Hospital, Chicago. 309 pages, 74 illustrations. J. B. Lippincott Company, Philadelphia, 1941.

**OPERATIVE SURGERY,** Including Anesthesia, Pre- and Postoperative Treatment, Surgical Technique, Blood Transfusion and Abdominal Surgery. Edited by Frederic W. Baneroff, M.D., F.A.C.S., Associate Clinical Professor of Surgery, Columbia University, etc. 1102 pages, illustrated. D. Appleton-Century Co., New York, 1941.

**COMPLETE WEIGHT REDUCER.** By C. J. Gerling. Harvest House, New York, 1941.

In summarizing this case report, the following statement was made:

"While, up to the present time, there is no definite evidence of an associated Lindau's syndrome in this patient, cases of this type should be followed by both x-ray and physical examination for evidence of pathology in the central nervous system or somatic organs."

On April 26, 1941, this patient was admitted to the Neuro-Surgical Service of the Brooklyn Hospital complaining of nausea and vomiting, increasingly severe headaches, and inability to get about because of unsteadiness of gait. A diagnosis of cerebellar tumor was made and on April 28, 1941, a posterior fossa craniotomy was performed.

In the left cerebellar lobe there was encountered a cyst containing approximately 30 to 40 c.c. of xanthochromic fluid. The cyst was evacuated, but no attempt was made to remove the cyst wall. The postoperative diagnosis was left cerebellar cyst, the postoperative course was uneventful, and the patient was discharged from the hospital on May 27, 1941. The discharge diagnosis: Angiomatosis retinae (von Hippel's disease) cerebellar cyst, left side (Lindau's disease).

MERVYN V. ARMSTRONG, M.D.

85 PIERREPONT STREET,  
BROOKLYN, N. Y.

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## Items

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### American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada on Saturday, January 3, 1942, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination will proceed automatically to the Part II examination held in June, 1942.

Candidates for *reexamination* in Part I (written paper and submission of case histories) must request such reexamination by writing the Secretary's Office not later than November 15, 1941. Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their original examination.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Atlantic City, N. J., in June, 1942, immediately prior to the annual meeting of the American Medical Association.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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### Fellowship in Public Health Obstetrics

The Alabama State Department of Public Health, in cooperation with the Children's Bureau of the United States Department of Labor, announces fellowships in public health obstetrics for physicians who have had a minimum of a year's rotating internship and one year of obstetric training. Training provided will embrace field work in already established maternity clinics in rural areas; in the organization of new centers and rotating through the various departments and projects connected with the obstetric aspects of public health. A stipend of \$150.00 a month plus travel while in the field is provided. Applications should be sent to Dr. J. N. Baker, State Health Officer, Montgomery, Alabama.

- Washington Gynecological Society.** *President*, R. L. Sylvester. *Secretary*, W. R. Thomas, 1830 K. Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, E. Lee Dorsett. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Galveston, Texas, September, 1941.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, H. C. Walser. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Francis R. Irving. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, T. M. Boulware, Birmingham, Ala. *Secretary*, John Newdorp, Montgomery, Ala. Next meeting Montgomery, Ala., April, 1942.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.

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### Erratum

In the article by U. J. Salmon et al., on "The Treatment of Abnormal Uterine Bleeding With Androgens," in the June, 1941, issue, page 1002, the heading, "value of methyl testosterone" should read "value of ethinyl testosterone." Attention is called likewise to errors in the list of references, pages 1008 and 1009, which correctly are as follows: (22) *J. Clin. Endocrinol.* 1: 554, 1941; (35) *J. Clin. Endocrinol.* 1: 62, 1941; and (69) *J. Clin. Endocrinol.* In press.

# ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(*Appears in January, April, July, October*)

- American Gynecological Society. *President*, W. C. Danforth, Evanston, Ill. *Secretary*, H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Next meeting, May, 1942, Sky Top, Pa.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting will be held at White Sulphur Springs, Va., September 9-11, 1942.
- Central Association of Obstetricians and Gynecologists. *President*, Thomas B. Sellers, New Orleans, La. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Next meeting, New Orleans, La., Fall of 1941.
- South Atlantic Association of Obstetricians and Gynecologists. *President*, R. A. Bartholomew, Atlanta, Ga. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February 6-7, 1942, Atlanta, Ga.
- A. M. A. Section on Obstetrics and Gynecology. *Chairman*, W. T. Dannreuther. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June, 1942, Atlantic City, N. J.
- New York Obstetrical Society. *President*, H. J. Stander. *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia. *President*, T. L. Montgomery. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society. *President*, Charles E. Galloway. *Secretary*, James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society. *President*, George G. Cochran. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society. *President*, Abraham Samuels. *Secretary-Treasurer*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society. *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society. *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology. *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society. *President*, Thomas Evans, Jr. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston. *President*, John Rock. *Secretary*, Judson A. Smith, 264 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.
- New England Obstetrical and Gynecological Society. *President*, Frederick L. Good. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society. *President*, John Vruwink. *President-Elect*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, Los Angeles, Calif., November 5 to 8, 1941.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

but universally given by physicians who are well acquainted with the danger signs of bleeding in the last trimester of pregnancy. In my community, as in many others, hospitalization of obstetric patients is practically universal, and transportation to the hospital is quickly accomplished. In 1890 Holmes<sup>2</sup> wrote, "Cesarean section will be of value in selected cases, but never will be popular, for the conditions and surroundings favoring celiotomy will seldom be at hand." This is no longer true in my community.

Notwithstanding recent papers by DeNormandie,<sup>3</sup> McGlinn and Harer,<sup>4</sup> Falls,<sup>5</sup> Montgomery,<sup>6</sup> and Stander,<sup>7</sup> we find that Irving,<sup>8</sup> and Holmes,<sup>9</sup> as late as 1937 and 1940, respectively, considered cesarean section as a dangerous method of delivery compared with the vaginal methods, and voiced the opinion that hysterectomy in such cases greatly increases the mortality. Holmes quotes Irving's tables showing 4.9 per cent mortality for the conservative type treatment as against 16.8 per cent mortality for cesarean section, and Irving in his review of the subject gives a mortality of 2.9 per cent for conservative as against 14.5 per cent for the cesarean method. Irving further states that since giving up the use of cesarean sections for this purpose at the Boston Lying-in Hospital there has been only one death since 1931. He quotes DeSnoo who gives 6 per cent mortality for the conservative treatment as against 33 per cent for the more radical method in cases where the placenta has about half separated.

I wish to protest against such use of mortality figures. This is not justified for two reasons: First, no account has been taken of improvement in the matter of transfusions and anesthesia; and second, it is obvious that cesarean sections, and especially hysterectomies, were done in the more serious type of case. Comparing such operative mortalities with those of the vaginal deliveries, where many cases of minor degree are included, is a fundamental statistical error. We have learned from studies of the end results of cancer treatment that we must compare groups of cases which, at the beginning of treatment, have arrived at similar stages of the disease, otherwise the comparisons of the results of one clinic with another are quite meaningless. The same holds true in this discussion.

The attitude of obstetricians at the Hartford Hospital is in line with that advocated by McGlinn and Harer,<sup>4</sup> which is briefly as follows: Delivery by the vaginal route is warranted only when delivery is actually immediately impending or may be promptly accomplished by use of an obstetrical maneuver. In all other cases cesarean section is indicated. Stander<sup>7</sup> puts it as follows: "most cases . . . except those in which the cervix is dilated and delivery can be quickly accomplished should be subjected to cesarean section." As will be seen from the various tables which follow, death of the fetus is not considered a contraindication to cesarean section. We believe that cesarean section is best used very early, as soon as the diagnosis is made, before the condition of the patient and of the uterus has become grave and if possible before the baby has died.

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## Original Communications

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### THE ROLE OF CESAREAN SECTION IN THE TREATMENT OF PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA\*

JAMES RAGLAN MILLER, M.D., HARTFORD, CONN.

IN 1870 Goodell<sup>1</sup> laid down as the principles of treatment for premature separation of the normally implanted placenta the dictum of Theodore Mayern that the uterus should be evacuated as soon as possible ("Praestantissimum remedium est foetus extractio"). Cesarean section has always appealed to the obstetrician as the most effective and rapid method of accomplishing this end. In the early days, however, patients were brought to the hospital after many hours of labor and in a state of shock so that all of the earlier writers reported high mortality rates for cesarean section as opposed to the vaginal method of delivery.

During recent years many factors have combined to reduce the dangers of cesarean section. The most important of these is the adoption of a carefully individualized anesthesia, given by the most skilled anesthetists available. Of equal importance is also the modern attitude toward operation in shock. It has been found that prompt and repeated transfusions can place an otherwise desperate patient in satisfactory condition to withstand operation.

In 1870 Goodell wrote "by far the most frequent symptom is an alarming state of collapse." This is not true today for there are many communities, in which my own is included, where prenatal care is all

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\*Read at the Sixty-sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

TABLE I\*

CESAREAN SECTIONS (59)										VAGINAL DELIVERIES (61)										
HISTORY NUMBER	SEPARATION	BLOOD LOSS	SHOCK	RIGIDITY	APOPLEXY	TOXEMIA	BABY	AGE	GRAVIDA	PARA	HISTORY NUMBER	SEPARATION	BLOOD LOSS	SHOCK	RIGIDITY	TOXEMIA	BABY	AGE	GRAVIDA	PARA
302973	4	3	4	0	3	0	SB	23	1	0	198796	4	4	4	4	0	SB	34	2	1
275539	4	3	3	3	4	0	SB	18	1	0	380959		3		2	0	SB	39	7	4
395456	4	3	3	3	4	0	SB	25	1	0	206764	4	2	1	2	0	SB	18	1	0
350751	4	3	3	4	2	?	SB	40	13	10	238126	4	2	0	4	ECL	SB	35	3	2
334078	4	3	3	?	1	0	SB	36	3	2	373128	4	2	0	0	1	SB	30	3	0
301501	4	3	2	0	3	2	SB	33	2	1	349719	4	2	0	0	?	SB	18	1	0
338648	4	3	0	4	2	3	SB	41	6	3	368412	4	2	0	0	0	SB	23	1	0
330660	4	3	0	4	2	0	SB	31	3	2	220077	3	3	0	3	0	SB	34	4	3
209568	4	2	0	4	2	2	SB	37	5	4?	393541	3	2	0	0	0	SB	33	3	2
367329	4	2	0	4	2	2	SB	30	1	0	200050	3	2	0	0	0	NN	30	6	3
336836	4	2	0	4	2	0	SB	28	3	2	236883	3	1	0	4	4	SB	37	7	?
266185	4	2	0	?	1	0	SB	32	3	2?	238131	2	3	0	2	0	SB	37	9	?
345707	3	3	2	4	2	0	SB	27	2	1	374116	2	2	0	0	0	L	22	1	0
301516	3	3	2	0	2	1	SB	25	1	0	293360	2	2	0	0	0	L	28	3	2
190241	3	3	0	4	3	0	SB	43	10	8	219135	2	2	0	0	0	SB	31	6	5?
309093	3	2	0	4	0	0	SB	27	3	2	356958	2	1	0	2	0	L	24	3	2
251247	3	2	0	3	0	0	SB	37	4	3	348922	2	1	0	0	0	SB	26	1	0
337193	3	2	0	2	2	0	SB	38	1	0	345403	1	3	0	0	ECL	L	22	0	0
321980	3	2	0	0	1	0	SB	36	3	2	369983	1	2	0	0	0	L	29	1	0
284842	2	3	2	4	0	?	L	32	7	5	395806	1	2	0	0	0	L	31	2	1
271346	2	3	0	1	2	0	SB	21	3	2	328296	1	2	0	0	0	L	28	2	1
397032	2	2	2	0	2	1	SB	36	7	4	325741	1	2	0	0	?	L	30	4	3
353462	2	2	1	4	?	0	L	31	1	0	328931	1	2	0	0	0	L	35	3	2
212284	2	2	1	?	?	0	L	26	1	0	314126	1	1	0	0	0	L	36	1	0
274529	2	2	0	3	2	1	L	33	2	0	271127	1	1	0	0	2	L	22	1	0
379874	2	2	0	2	0	0	L	38	3	?	373517	1	1	0	0	0	L	31	1	0

It is obvious that clinics where most of the patients are brought in late in labor, and in bad condition, have been prejudiced against cesarean section and in favor of vaginal methods. Teachers of obstetrics who are preparing practitioners for home deliveries will accent those maneuvers which the practitioner must know how to perform in the absence of ideal surroundings. We believe, however, that the deliberate choice of the vaginal method of delivery early in labor and where ideal surroundings are present is justified neither by our clinical experience nor by our understanding of the progressively malignant process which is going on in the uterus.

#### MATERIAL

The present review is a study of 120 cases which have been found on careful search of the records of the Hartford Hospital from Oct. 1, 1916, to Oct. 1, 1940. These dates were chosen because my experience in the hospital covered this period and my previous studies of hospital histories have been made on admissions since 1916. In all fairness it should be said at the outset that one death following cesarean section done for premature separation of the placenta is recorded in the year 1914. This is the only such death in the hospital's cesarean section experience. The patient was severely toxic, was operated upon by an interne under staff supervision, while in shock, with gas-oxygen-ether anesthesia. Both the mother and baby died, the mother surviving the operation by two hours. Prior to 1916 adequate records do not permit statistical study in this field. During the years covered by this study, hospital deliveries increased from 985 to 2,371 per year. Eleven hundred and sixty-two cesarean sections were performed from 1927 to 1940: 4.6 per cent for placenta previa and 4.7 per cent for premature separation of the placenta. During the last nine years the incidence of cesarean section for the whole clinic was 5.0 per cent, and the mortalities for 883 cesarean sections was 0.68 per cent. Since the last death after cesarean section, there have been, up to Oct. 1, 1940, 332 consecutive cesarean sections without a death. It will be appreciated, therefore, that cesarean section is done on very liberal indications. While it is undoubtedly true that some of the cesarean sections done for premature separation might have been avoided in favor of vaginal delivery, adverse criticism cannot be based on our mortality record.

Table I is a synopsis of the individual case histories. It will be noted from the hospital history serial numbers that the use of cesarean section, especially in the more serious cases, is a development of the more recent years. It will be noted that very few such diagnoses were made prior to 1926, the histories of which period are numbered below 200,000. For the years prior to 1926 all cases which had cesarean sections are listed, whereas it is probable that many of the milder cases delivered by the vaginal route failed to be included. The omission of these cases prior to 1926 does not materially change the enumerations. This table arranges the cases in what we believe to be the order of their severity, giving primary consideration to the estimate of the degree of separation. The scale of one to four is used in which one is the least and four the greatest. The secondary items of arrangement concern the estimated blood loss, shock, the degree of rigidity, and in cesarean section cases the degree of apoplexy. In the absence of such accurate data as those



who work in University clinics are accustomed to find, it is obvious that certain errors in assigning the degree of severity for all these factors may creep in. Sufficient records, however, were available to furnish a shrewd guess for the purposes of this study.

Table II summarizes Table I and clearly shows that in all enumerations, except toxemia, the more serious cases tended to be handled by cesarean section and the less serious by the vaginal route.

TABLE II. PREMATURE SEPARATION OF THE PLACENTA, HARTFORD HOSPITAL 1916-1940  
Comparison (by Grades) of Cesarean Section vs. Vaginal Deliveries

GRADES	VAGINAL	CESAREAN	GRADES	VAGINAL	CESAREAN
<i>Separation</i>			<i>Rigidity</i>		
4	7	12	4	3	11
3	4	7	3	2	6
2	6	18	2	1	8
1	34	18	1	0	2
?	10	4	0	53	24
	61	59	?	2	8
				61	59
<i>Blood Loss</i>			<i>Toxemia</i>		
4	1	1	Ecl.	2	1
3	4	13	4	2	0
2	16	34	3	2	3
1	33	10	2	4	6
?	7	1	1	2	5
	61	59	0	45	44
			?	4	0
				61	59
<i>Shock</i>					
4	1	1			
3	0	4			
2	0	7			
1	2	3			
0	56	44			
?	2	0			
	61	59			

Table III shows the division according to the number of pregnancies and the duration of gestation.

TABLE III. PREMATURE SEPARATION OF THE PLACENTA  
HARTFORD HOSPITAL 1916-1940

Total	120	Private	79	Ward	41
Gravida i				50	
Gravida ii-v				54	
Gravida vi and over				16	
Gestation up to 28 wk.				9	
Gestation 29 to 31 wk.				2	
Gestation 32 to 35 wk.				21	
Gestation 36 and over				83	
Not stated				5	

Table IV shows the number of the various grades of toxemia. It is highly probable that, in the five instances where toxemia was not stated, the degree was either "zero" or "one." It would seem from this table that private patients received closer prenatal supervision than ward cases.

[illegible]

\*SB, signifies stillbirth; NN, neonatal death; L, discharged alive; EOL, eclampsia; ?, insufficient data.

this series there is very little difference in the number of live babies which were discharged from the hospital after the neonatal period. It is also evident, as it was in Table I, that cesarean sections were done more frequently in the serious cases.

Table VIII shows the comparison of our cases with those of the Boston Lying-in Hospital, published by Goethals.<sup>10</sup> A strict comparison of these two series should not be made, for the greater number of the Hartford Hospital group was handled in the fourteen years after the Boston series ended. The number of primiparas in our series is appreciably greater. The periods of gestation and the number of non-toxic cases are almost identical. The greater number of eclampsia, cesarean section deaths, fetal deaths, maternal mortality, and severe degrees of detachment and rigidity in the Boston series undoubtedly indicate to some extent the greater severity of the cases in the early period.

TABLE VIII. PREMATURE SEPARATION OF THE PLACENTA, HARTFORD HOSPITAL 1916-1940

Boston Lying-in Hospital and Hartford Hospital Series Compared

	B.L.-I. 1916-26	H.H. 1916-40
Total	128	120
Gravida i	39	50
36 weeks +	85	83
Nontoxic	91	88
Eclampsia	6	3
Cesarean section (deaths)	39-(3)	59-(0)*
Rigidity (3 and 4)	42	22
Detachment (4)	35	21
Mothers died	11	2
Fetus died	80	52

\*One death after cesarean section in 1914. (The only such death in the Hartford Hospital cesarean history.)

Objection can be raised against the use of cesarean section where vaginal delivery might be employed on the score that subsequent child-bearing will be diminished. Table IX shows that our experience in this regard does not bear out such criticism. Whatever limitation to subsequent childbearing might have been caused by the employment of cesarean section, there was still greater loss of subsequent productive fertility in cases where cesarean section was not employed.

TABLE IX. PREMATURE SEPARATION OF THE PLACENTA, HARTFORD HOSPITAL 1916-1940

Subsequent Pregnancies in Patients Delivered as Shown Prior to Oct. 1, 1939.  
Comparing Cesarean vs. Vaginal Deliveries

	CESAREAN SECTION	VAGINAL
Total	49	51
Hysterectomies	6	0
Sterilized	1	0
Possibly fertile	42	51
No known pregnancies	29	41
Subsequently pregnant	13	10
Subsequent pregnancies	17	11
Live babies	13	7
Subsequent cesarean section	11	2
Subsequent premature separation	3	3

TABLE IV. PREMATURE SEPARATION OF THE PLACENTA  
HARTFORD HOSPITAL 1916-1940

Toxemia	Grade	0	88
		1	7
		2	10
		3	5
		4	5
	Not stated		5
	Eclampsia		3
Private cases with no toxemia			90%
Ward cases with no toxemia			70%

Tables V and VI attempt to analyze the relationship between toxemia and hemorrhagic infiltration of the uterine muscle in cesarean sections. It is clearly evident that severe toxemia, in our experience, has played a very small part in the production of the uterine lesion.

Table VII shows comparison of the fetal loss by the two methods of delivery according to the degree of separation of the placenta. For

TABLE V. PREMATURE SEPARATION OF PLACENTA, HARTFORD HOSPITAL 1916-1940  
Cesarean sections 59      Toxic 15

TOXEMIA GRADE	APOPLEXY GRADE					TOTAL
	0	1	2	3	4	
0	24	5	11	2	2	44
1	2	0	3	0	0	5
2	2	1	2	1	0	6
3	1	0	2	0	0	3
4	0	0	0	0	0	0
Eclampsia	1	0	0	0	0	1
	30	6	18	3	2	59

TABLE VI. PREMATURE SEPARATION OF PLACENTA, HARTFORD HOSPITAL 1916-1940  
Cesarean sections 59. Apoplexy (hemorrhagic infiltration of uterine muscle) 29

APOPLEXY GRADE	WITH TOXEMIA	NONTOKIC
1	1	5
2	7	11
3	1	2
4	0	2
	9	20

TABLE VII. PREMATURE SEPARATION OF THE PLACENTA, HARTFORD HOSPITAL  
1916-1940

Fetal Loss by Cesarean Section vs. Vaginal Deliveries  
(By Degree of Separation of the Placenta)

DEGREE OF SEPARATION	METHOD OF DELIVERIES		LIVE BABIES		STILLBIRTHS		NEONATAL DEATHS	
	C.S.	VAG.	C.S.	VAG.	C.S.	VAG.	C.S.	VAG.
1	18	35	14	30	2	3	2	2
2	18	6	15	3	2	3	1	0
3	7	4	0	0	7	3	0	1
4	12	7	0	0	12	7	0	0
?	4	9	3	3	1	4	0	2
Totals	59	61	32	36	24	20	3	5

## DISCUSSION

The necessity of removing the uterus has undoubtedly been exaggerated and our group in Hartford is convinced that too many uteri have been removed. The conservative school has shown that hemorrhage seldom persists after the uterus is emptied. We recall, however, the case reported by Frank<sup>13</sup> of a severe Couvelaire uterus emptied by low classical cesarean section. Pituitrin was injected into the uterine muscle and a firm uterine and vaginal pack was later employed which failed to stop the bleeding. Hysterectomy was done six hours after the cesarean section and the patient survived, due undoubtedly to repeated transfusions. Urine and blood pressure were normal.

Some hysterectomies have been done as the easiest way to sterilize where this was desirable. Where the hemorrhagic process has extensively involved the wall of the uterus, it has been removed, having in mind the disastrous results of necrobiosis of the uterine muscle reported by Coventry and Moe.<sup>14</sup>

Since we have been doing cesarean sections very early and have observed the hemorrhagic lesion in the absence of toxemia, trauma or other discernible factors, we have become dissatisfied with the many explanations of etiology which have been advanced, and it is suggested that renewed efforts be made to study the blood vessel lesions not only in the late but in the early cases, making use of recently developed injection and special staining techniques. It is not yet clear why the separation of the placenta within the uterus should cause hemorrhagic infiltration which is invariably confined to the outer and not the inner layers of the uterus. May we not be dealing with a process which should be investigated as a result of isoimmunization reactions, bringing this lesion in line with many spontaneous abortions, misearriages, and unexplained fetal deaths, and perhaps with erythroblastosis fetalis? (Levine, Katzin, Burnham.<sup>15</sup>)

## CONCLUSIONS

1. Indications for cesarean section in the treatment of premature separation of the normally implanted placenta should be extended wherever ideal conditions are obtainable.

2. Under ideal surroundings cesarean section, even in the presence of shock, can be safely employed, provided adequate methods are used to combat shock by transfusions and fluid administration, and provided the operation is skillfully performed under expertly administered anesthesia which is suited to the patient's needs.

3. Experience of the Hartford Hospital over many years has shown that cesarean section can be employed without increase in mortality and without severely limiting subsequent childbearing, and further that in the presence of a live child, fetal losses are greatly diminished.

4. Attention is called to the inadequacy of a purely anatomic division between premature separation of the normally implanted placenta and placenta previa.

Objection to the cesarean method may be raised also on the score of danger of rupture of the uterine scar in subsequent pregnancies. The records of all subsequent pregnancies were studied and in only one instance was there observed a poorly healed uterine incision. [In that instance I had personally sutured the uterus with care. The uterus was not hemorrhagic in any degree, nor was the patient toxic, and the failure of adequate healing cannot in my opinion be ascribed to anything but the cesarean method.] In this case, however, a subsequent cesarean section was done at the time of election without a rupture of the uterus, and a live baby was obtained.

#### MORTALITY

The two deaths recorded in this series were of patients who were delivered by the vaginal method. A synopsis of these cases is given.

CASE 1.—In 1920 a private case of a general practitioner, gravida vii, para vi, 28 years of age. She bled severely on admission and after delivery. Her total labor lasted six hours. She was packed before admission, following which the packing was removed, bag inserted and manual dilatation was performed. A still-born fetus was delivered spontaneously under chloroform anesthesia. The patient died on the fourth day, her temperature having risen to more than 100.4° F. on one day only. Albumin and casts were present in large amounts, and she died with the appearance of cardiac decompensation with pulmonary edema.

CASE 2.—The second patient, gravida ii, para i, 34 years of age, was delivered in 1927 (private case of an obstetrician). She came in promptly after the onset of pains which awakened her from sleep. The pains were accompanied by considerable blood loss. On admission the cervix was dilated manually from one to three fingers. The edge of the placenta was felt and the membranes were ruptured, allowing the head to descend. Bleeding then stopped. It was noted, however, that the uterus was boardlike, and when she delivered spontaneously (six hours after onset of labor), a stillborn baby and placenta were extruded with a very large amount of fluid and clotted blood. In spite of uterine tamponade which was carried out twice, the patient died (ten hours after the first pains) before a transfusion could be arranged. The diagnosis in this case was both a placenta previa marginalis and premature separation of the low-lying placenta. An autopsy was not obtained.

This second death recalls the cases presented by Rudolph<sup>11</sup> in which he was able to observe at cesarean section a typical hemorrhagic uterus and found the placenta attached to the lower posterior wall. Not only Rudolph but Montgomery<sup>6</sup> and Kellogg<sup>12</sup> report that numerous such instances of premature separation with low-lying placenta are encountered. Such cases raise the question as to whether the classical definition of this condition is fully justified. I do not agree, however, with Montgomery that these cases with retroplacental hematomas, spasm of the uterus, and hemorrhage in the muscle should be called placenta previa.\*

In his paper on "Ablatio Placentae," Holmes<sup>9</sup> said "failure to find the placenta within reach of the finger makes the diagnosis certain. In placenta previa the discovery of the afterbirth is positive, no pain so characteristic of ablatio is present, and no distention is met with." His definition recognizes only anatomic boundaries, viz., if the placenta has attached above that portion of the uterus which must dilate, the case is properly called ablatio. It would seem that this definition does not include some of the undoubtedly typical cases.

\*It would be convenient for us to use the customary classification, for if we did so our whole series would present no death since 1920.

type. Eclampsia and toxic ablatio have poisons bathing maternal and fetal tissues, great nervous depression and coma, destruction of nephritic and hepatic tissue with an arrest of function. As a result of their similarity it is as illogical to perform cesarean sections for ablatio as for eclampsia. It is needless to state contributory indications may make a section imperative.

There is a clear trend of the world's experts to limit, even to discard, cesarean section for all types of placental separation. The experience of the Rotunda Hospital, and of Irving is indicative of this trend. As late as 1939 the French Obstetrical Congress devoted a lengthy session to the consideration of placental separation. In 1,000 cases they reported the mortality following sections was 19 per cent, and for the conservative vaginal handling it was 6 per cent. Furthermore, in no sense is hysterectomy an essential part of the management, although special circumstances may require it.

So far as we know there is nothing in the physiology or anatomy of the normally implanted placenta which would lead to a toxic or nontoxic premature separation, and prevent an associated separation in placenta previa. The prompt escape of the blood in placenta previa prevents uterine distention from retained blood. The relative absence of case reports of toxic apoplexy with placenta previa must be ascribed to a lack of observation.

DR. RAYMOND E. WATKINS, PORTLAND, ORE.—During the ten-year period from 1931 to 1941, there have been 9,051 deliveries of pregnant women in the Obstetric Clinic of the University of Oregon Medical School. All were indigent patients. Premature separation of the placenta was diagnosed clinically in 30 instances. All gestations were twenty-eight weeks or more. In 24, premature separation was proved by pathologic examination, making a true incidence of one to 377. Of the remaining 6, three showed no evidence of separation on examination of the placenta, and in 3 others the placenta unfortunately was not described. All 6 patients had had typical symptoms and findings previous to delivery.

We divided our cases according to the degree of severity into (a) mild, 2; (b) moderate, 14; and (c) severe, 8.

There was a noticeable lack of prenatal supervision in these patients, 9 having none before admission to the hospital, and 10 inadequate care. Fifteen of our 24 patients showed an absence of the fetal heart beat upon admission to the hospital after symptoms of placental separation had occurred, making live birth possible in but 38 per cent.

The bleeding occurred vaginally in 21, but in 3 it was concealed. Only one with concealed hemorrhage was considered a severe case and a low cervical section was performed in this instance.

The degree of separation was partial in 21 and complete in 3. Fourteen patients entered the hospital in active labor. Twenty-one were delivered vaginally while 3 required cesarean section. The low cervical operation was performed in each instance.

The summary of our treatment is as follows: (1) Twenty-one treated expectantly; (2) membranes ruptured 8 times as a method of controlling bleeding and to induce labor; (3) forceps used in 3 patients; (4) blood transfusions in 6 patients; (5) low cervical sections in 3 severe cases; (6) manual dilatation of the cervix was not done, nor were bags used to dilate the cervix in any case.

Our maternal mortality, 4.1 per cent, consisted of one patient, who was delivered vaginally. She was a para ii who suddenly began to hemorrhage three hours after delivery with complete placental separation and died while the uterus was being packed. In retrospect we think this patient might have been saved had the uterus been packed immediately following delivery.

Eight, or 33½ per cent, of our 24 babies were born alive, but one premature baby died thirty-six hours after birth.

The management of patients with premature separation of the placenta has been a much disputed subject. There are those who advocate active interference early, in an effort to save both mother and child, and others who treat all patients conservatively. Both claim equally good results. Certainly no criticism could be made of the maternal and fetal mortality in the large series of cases Dr. Miller has presented, for his results are remarkable, both as to fetal and maternal survivals.

5. Hope is expressed that observation of early lesions with study of the vascular lesions by modern methods may furnish us with a clearer understanding of etiology.

#### REFERENCES

- (1) *Goodell, W.*: Am. J. Obst. 2: 281, 1870. (2) *Holmes, R. W.*: Am. J. Obst. 44: 753, 1901. (3) *DeNormandie, R. L.*: AM. J. OBST. & GYN. 31: 325, 1936. (4) *McGlinn, J. A., and Harer, W. B.*: Ibid. 30: 226, 1935. (5) *Falls, F. H.*: Journal-Lancet 54: 107, 1934. (6) *Montgomery, T. L.*: Discussion of DeNormandie's paper q.v. (7) *Stander, H. J.*: Curtis' Obstetrics and Gynecology 2: 445, Philadelphia, 1934, W. B. Saunders Co. (8) *Irving, F. C.*: Int. Abst. Surg. 67: 56, 1938. (9) *Holmes, R. W.*: Am. J. Surg. 48: 61, 1940. (10) *Goethals, T. R.*: AM. J. OBST. & GYN. 15: 627, 1928. (11) *Rudolph, L.*: Ibid. 32: 479, 1936. (12) *Kellogg, F. S.*: Ibid. 15: 357, 1928. (13) *Frank, C. W.*: Ibid. 33: 512, 1937. (14) *Coventry, W. A., and Moe, R. J.*: Ibid. 25: 859, 1933. (15) *Levine, P., Katzin, E. M., and Burnham, L.*: J. A. M. A. 116: 825, 1941.

#### DISCUSSION

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—Those who have written on ante-partum placental separation have erected a structure of hypotheses elaborated from presumptive evidence, and based upon conjectural notions as to the etiology. Truth will be derived only when there shall be a discovery of the specific etiologic factors. Dr. Miller and I disagree on many fundamentals. In fact, the tenor of his paper, reflecting the experience and observation of the Hartford Hospital Staff, tends to controvert the prevalent concepts held by most authorities.

An analysis of his tables reveals that practically all of his cases were definitely benign, in sharp contrast to the tragic cases reported by most writers on the subject. It is noteworthy that there is an entire absence of the tetrad in any single patient of severe toxemia, severe hemorrhage, excessive shock and complete placental separation. He makes no mention of excessive distention or severe uterine pain, which are both characteristic of ablatio. Toxemia was noted in only 27 (23.9 per cent) of his 120 case reports. No mention is made of the Couvelaire utero-placental apoplexy.

The relative mildness of Dr. Miller's complications may be ascribed to a high order of prenatal care in Hartford, for 98.8 per cent of all parturients in 1938 were attended by physicians, and 98.4 per cent of such patients were confined in four hospitals. In the same year the Hartford Hospital housed 54 per cent of all the city births. Ablatio occurred 79 times in private, and 41 times in ward patients, which reverses the figures for relative frequency supplied by most authorities. Hartford is a commercial city with a notable absence of a large population domiciled in tenement and slums, which may account for the differences from the type of patients seen in large municipal hospitals of maritime or manufacturing cities.

Dr. Miller's tabulation of the cases of uterine apoplexy has put my mind in a quandary, for, so far as I am aware, every authority has maintained that apoplexy was invariable evidence of a Couvelaire type of separation. The enthusiasts for cesarean section have indeed defended the operation on the score that by this means alone a diagnosis of a true uteroplacental apoplexy might be made. In Dr. Miller's report of 59 sections 57 had notations regarding apoplexy, and this condition was noted in 28 cases as being present, only 9 of which were of toxic origin. Dr. Miller states, "It is not yet clear why the separation of the placenta . . . should cause hemorrhagic infiltration which is invariably confined to the outer, and not the inner, layers of the uterus." It may be conceived that trauma might produce such ecchymotic spots, but so far as I am aware this does not hold true of toxic apoplexies. All layers are involved, especially in the site of the placental attachment. It is the extravasation of blood in the serotina which inaugurates separation and the placental cotyledons participate in this hemorrhagic infiltration.

The elimination of eclampsia as an indication for section has probably contributed more to the lessening of the mortality of the disease and of the section than all the improved therapy of the one, and the bettered technique of the other. There is a peculiar analogy between eclampsia and ablatio, and specifically for the toxic



Eclampsia and separation of the normally implanted placenta are fundamentally of the same nature. The latter is preceded by typical manifestations of toxemia in the majority of cases, and the pathology in the placenta is identical with that of eclampsia. However, in separation of the placenta, we are confronted with two complications: hemorrhage and a marked tendency to shock, the latter being particularly dangerous.

I believe that the employment of conservative treatment is most important. By that I mean when the patient is first seen, dismiss the idea of delivering her, but rather give supportive treatment with glucose solution, whole blood or plasma intravenously, along with sedatives. Following improvement in her condition, rupture the membranes, apply an abdominal binder if necessary, and await within reason a spontaneous delivery. This will obtain much better results than if we rush in immediately with operative procedures. I think the impression should go out, particularly to the average man, that this is a condition which he can treat with greater success by conservative methods regardless of surroundings.

This is a case of separation of the placenta. You see the dark areas of acute infarction scattered through the whole strip identical in every way with those seen in eclampsia. The consistency and similarity of the placental findings in each condition have been such as to make me realize that cases of separation of the placenta are practically all on a toxic basis and that the cases due to trauma are negligible.

DR. MILLER (closing).—If our experience has served anything, it is to show that where one is confronted with a severe ablatio and what you would all recognize as an absolute indication for cesarean section, you can still do a cesarean safely if you pay attention to the fundamentals of blood loss replacement and anesthesia. Our experience has not met with the forebodings of those who have threatened us with dire consequences.

We had one death three weeks ago, since this series ended. That patient had had a systolic blood pressure of over 200 for more than three years and died with massive cerebral hemorrhage two hours after the cesarean section was done under block anesthesia, with a substitution of 1,000 c.c. of citrated blood. Personally, I should not have done a cesarean section in this case, though I believe that the operation had little to do with her death.

In our own experience we have not thought it advisable to do so many cesarean sections. The chance of error in early diagnosis is not inconsiderable. In 3, or 11 per cent, of our patients, the clinical diagnosis was not substantiated on examination of the placenta. . The early death of the fetus is also worthy of comment in this connection. Should the woman with slight or moderate premature separation who has a dead baby be subjected to section, if by conservative measures such as artificial rupture of the membranes, the hemorrhage can be controlled? Prompt transfusions will restore her blood loss. If no further hemorrhage occurs, this method seems to us the logical one to follow.

There is a high percentage of toxemia found in every group studied. Such patients do not tolerate major surgery well. With added blood loss their risk is undoubtedly increased. The severe separation may force our hand to do a section, but, for the mild or moderate case, it has been our policy to treat the patient conservatively, delivering vaginally if possible.

Regardless of the method of delivery used the resistance of the patient must be brought to the highest level, by the arrest of hemorrhage, repeated transfusions, and other supportive treatment. Each patient presents an individual problem, and the method of management must be determined in each case by the degree of separation and the condition of the patient. No hard and fast rule can be established.

DR. JAMES R. MCCORD, ATLANTA, GA.—I would like to present 92 cases of separation of the placenta, all of which were delivered from below and the great majority of them spontaneously. The total mortality was approximately 6.5 per cent.

In my opinion, in evaluating mortality in premature separation of the placenta, the condition should be divided into three groups, mild, moderate, and severe, and each group discussed separately. I do feel very strongly, and more so as the years go by, that a severe separation of the placenta is not only not an indication for a cesarean section, but is an indication for conservative treatment.

Tables I and II show our results.

TABLE I. ABRUPTIO PLACENTAE, 92 CASES

	MILD	MODERATE	SEVERE
Number of cases	46	30	16
Multiparas	71	80	87.5
Hypertension	41	66	62.5
Albumin	38	50	53
External hemorrhage	98	80	81
Shock	4.3	36	100
Rigidity	78.5	96	100
Spontaneous delivery	96	90	93
Fetal loss	54.3	76	93
Mortality	0	6.6	31

TABLE II

CAUSES OF DEATH		OPERATIONS	
Eclampsia	2	Low forceps	3
Lobar pneumonia	1	Version and extraction	3
Uremia	1	2 Shoulder presentations	
Cardiac decompensation	1	1 Transverse presentation	

DR. RUDOLPH A. BARTHOLOMEW, ATLANTA, GA.—Several decades ago, it came to be realized that the employment of forcible measures of delivery, such as internal version and extraction, manual dilatation of the cervix, difficult forceps delivery or cesarean section, was a large factor in the high mortality of eclampsia. Substitution of supportive measures, induction of labor, and a minimum of trauma effected a reduction in mortality from the figures of 15 to 20 per cent to 5 to 7 per cent. We are coming to the same viewpoint in regard to separation of the placenta.

interspinous ligaments, were able to produce syndromes typical of anginal and renal colic. Because of these findings they stated that "all the chief subjective phenomena usually associated with visceral disease

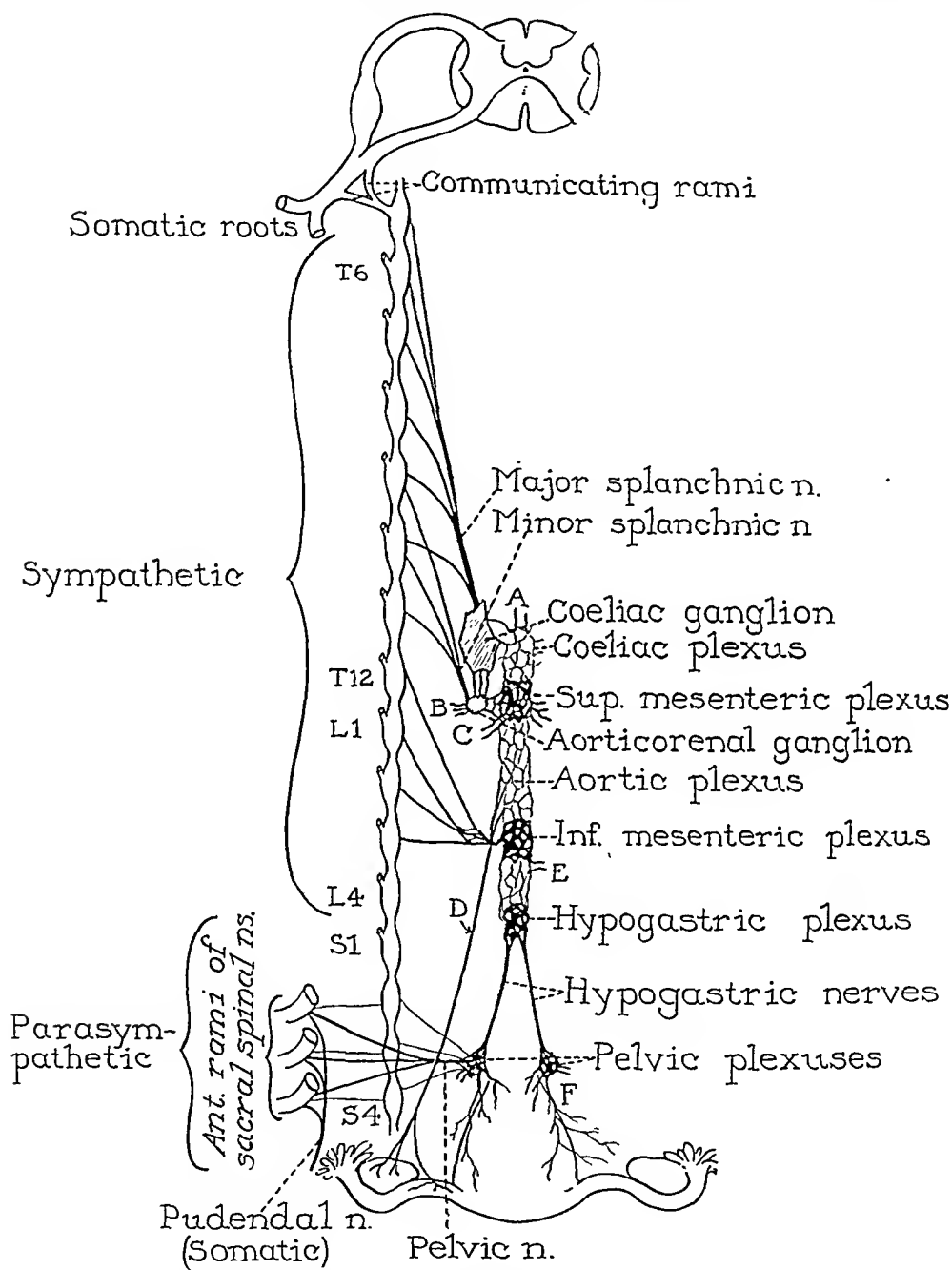


Fig. 1.—Anatomic distribution of the somatic and autonomic nerve fibers of concern to the gynecologist. A, Fibers to esophagus, stomach, duodenum, pancreas, liver, gall bladder and spleen; B, to kidney; C, to small intestine, cecum, ascending and transverse colon; D, to ovary and Fallopian tube; E, to sigmoid and descending colon; F, to rectum, bladder, and uterus. Somatic roots supply abdominal wall and parietal peritoneum. Pudendal nerve supplies perineal structures.

can be reproduced through purely somatic channels, [which] is opposed to the concept that somatic and visceral pain are to be regarded as separate entities." These authors concluded that, "the pain of visceral and

## PELVIC PAIN\*

### A FOLLOW-UP STUDY

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IN ASSEMBLING data for a previous paper<sup>15</sup> on pelvic pain it was found that approximately one-sixth of the women who consulted physicians at the Mayo Clinic in 1936 had ailments concerned with pain in the region of the pelvis. For that study, the records of 500 of these women were analyzed and data were obtained on each patient's age and civil state, on the site and frequency of the pain, and on the physical findings and diagnosis. In this present paper the subject of pelvic pain is reviewed briefly. Then the results are given of a study concerning relief of pelvic pain following treatment. Included in the study were those of the 500 patients who were living four years or more after the time of the previous study and concerning whom information could be obtained.

### PELVIC PAIN

Illustrations of the nervous system commonly found in textbooks may fail to show the continuity that exists between the innervation of the pelvic viscera and that of the abdominal viscera and the somatic structures.<sup>1, 6, 7, 12</sup> Fig. 1 illustrates the anatomic distribution of the somatic and autonomic (sympathetic and parasympathetic) nerve fibers which are of concern to the gynecologist. It is to be noted that the autonomic nervous structures form a closely integrated system of nerve fibers; that the sympathetic chain supplies fibers for all the abdominal viscera and that there are numerous levels at which impulses can leave or enter the sympathetic chain and the central nervous system. The human body is an integrated whole and nerve fibers pass to and come from viscera such as the stomach, colon, and pancreas, as well as from the uterus and its adnexa.

The so-called sympathetico-sensory fibers are the fibers which carry pain impulses from the pelvic viscera and are, therefore, most important to this discussion.<sup>5, 18</sup> In a strict physiologic and pharmacologic sense, these fibers have nothing in common with the true sympathetic nervous system. They are simply sensory fibers which have their cell stations in the posterior root ganglia and differ in no way from somatic sensory fibers except that they pass to the spinal cord through the anatomic sympathetic system. Properly they should be termed viscerosensory fibers.

With the foregoing facts in mind, it is less unexpected than otherwise to learn that Lewis and Kellgren, by injecting saline solution into the

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tion of many of the pains and discomforts suffered by patients who reveal clinical evidence of chronic nervous exhaustion or constitutional inadequacy. These patients are so worn by their cares or exhaustion that the minimal impulses received from the viscera are not inhibited at the customary level in the spinal cord; consequently they are suffering, more or less constantly, from some pain or discomfort.

#### THE FOLLOW-UP STUDY

This follow-up study of pelvic pain was attempted with the full realization that pain is not a diagnostic entity and that treatment or operation is ordinarily carried out for the relief or cure of a pathologic condition rather than primarily for the relief of any one symptom, such as pain. However, it seemed to be desirable to know the percentage probability of relief of pain associated with various pelvic disorders.

At the risk of repetition of some material included in the opening paragraph, it should be said here that four or more years following examination of them in 1936, questionnaires were sent to the 500 patients included in the previous study.

Each patient was asked whether the pain was completely relieved, partly relieved, or not relieved. If the patient was not treated or operated upon at the clinic she was asked concerning whatever subsequent treatment or operation she may have undergone. Replies were received to 310 of the 500 questionnaires or 62 per cent. Twenty-three patients had died during the interval of four years and were excluded from the study. Therefore, the statistics are based on 310 patients.

TABLE I. CONDITION RELATIVE TO PAIN OF ALL PATIENTS AND OF PATIENTS WHO MADE CERTAIN COMPLAINTS

PAIN, AS REPORTED ON FOLLOW-UP	TOTAL PATIENTS FOLLOWED		PATIENTS WHOSE COMPLAINT ON FOLLOW-UP WAS OF:							
			LOWER ABDOMINAL PAIN		BACKACHE		MENSTRUAL PAIN		MULTIPLE COMPLAINTS	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Complete relief	131	43	91	47	14	26	13	45	13	38
Partial relief	91	29	50	26	23	43	9	31	9	27
Same as, or worse than, 4 years before	88	28	52	27	17	31	7	24	12	35
Total	310	100	193	100	54	100	29	100	34	100

#### RESULTS IN GENERAL

The over-all results are represented in Table I. This tabulation was made without regard to the original diagnosis or to the type of treatment which was employed. To simplify the tabulation further, all patients who had lower abdominal pain were grouped together, as were those who had backache, or dysmenorrhea, or multiple causes of complaint. Of the 310 patients, 193, or almost 62.3 per cent, complained primarily of lower abdominal pain. The remaining 37.7 per cent complained of backache or menstrual pain, or they made multiple complaints. The general statement can be made that, regardless of situation of their original pain, nearly three of every ten patients had not obtained relief.

somatic disease is derived from the direct stimulation of a common system of nerves, which supply all the deep lying somatic tissues concerned and by way of the anatomical sympathetic, also supply a limited amount of the tissues contained within the visceral peritoneum; and . . . these painful impulses are either identical with, or are generally associated with the afferent impulses which set up reflexly a common series of motor and sensory reactions." This statement is contrary to the older hypotheses of Lennander, Ross, Mackenzie,<sup>10, 11</sup> Head and Morley,<sup>13, 14</sup> but it would seem factual.

In the evaluation of pain in general it is well to remember that some of the different sensations are attributable to stimulation of special, differentiated end-organs of nerves, such as encapsulated<sup>17</sup> end-bulbs for touch, or the Meissner corpuscles for touch and pressure. However, sensations of pain occur, owing to stimulation of free, undifferentiated nerve fibers. As the visceral supply of such nerve fibers is sparse, and because nerve fibers and cells which supply the viscera are much smaller than those which supply somatic structures, it is not difficult to understand the difference in the efficiency of sensations of pain when the viscerosensory and somaticosensory systems are compared. Because of this difference it must be true that viscera are insensitive to stimuli unless such stimuli are massive and that localization of visceral pain is somewhat vague.

It has been shown<sup>9</sup> that the viscera are insensitive to ordinary stimuli such as burning and crushing but are sensitive to such stimuli as an increase in tension. Tension in the tissues may be caused by inflammation, edema, or vascular engorgement. It is an obvious but seldom appreciated fact that inflammation can exist without causing pain. In other words, there are painful and painless types of inflammation. Kinsella<sup>3, 4</sup> has well illustrated this by recalling that an acutely inflamed appendix is painful because the appendix is hard and under tension but an acute gastric ulcer is not painful until induration and tension occur. A striking example is the disappearance of pain after incision of an abscess; the inflammation is there both before and after incision but the pain disappears with the decrease in tension.

Another important physiologic concept is that sensory impulses received in the posterior horns are integrated at the level where they are received; they may be inhibited or relayed.<sup>19</sup> As far as the somatic sensory apparatus is concerned it is unlikely that, under ordinary circumstances, the end-organs of the discriminative senses (touch temperature and so on) could be stimulated without, at the same time, the pain receptors being stimulated. Yet the sensations of the discriminative senses reach the level of consciousness while those of pain may not, because of being inhibited in the posterior horns of the spinal cord. It would seem that this same finding applies to impulses which are received from the viscera. This is of particular clinical importance, because this inhibition of painful impulses may be weakened by worry, chronic exhaustion, or general ill health. Under such circumstances potential pain stimuli, which ordinarily would be unnoticed, reach the consciousness of the individual with abnormal ease. It is likely that this is the explana-

that about 6 of 10 patients were entirely relieved of pain by surgical measures, the pain of 2 of 10 was improved, and that of another 2 of 10 was the same as four years before or worse.

TABLE III. EFFECT ON PAIN OF SURGICAL TREATMENT COMPARED WITH THAT OF NONSURGICAL TREATMENT

PAIN AS REPORTED ON FOLLOW-UP	PATIENTS TREATED AND FOLLOWED			
	SURGICALLY		NON-SURGICALLY	
	NO.	%	NO.	%
Complete relief	77	58	54	30
Partial relief	27	21	64	36
Same as, or worse than, 4 years before	27	21	61	34
Total	131*	100	179†	100

\*Eleven patients excluded; died in the interval of four years.

†Twelve patients excluded; died in the interval of four years.

In Table III comparison is made, on the basis of relief of pain, between patients subjected to surgical treatment and those subjected to medical treatment. Evidently, of patients treated surgically, a larger percentage (79 per cent) were completely or partly relieved than was true of those

TABLE IV. EFFECT ON PAIN REPORTED BY PATIENTS WHO HAD RECEIVED CERTAIN DIAGNOSES

DIAGNOSIS	TOTAL ORIGINAL DIAGNOSES*	PAIN AS REPORTED ON FOLLOW-UP					
		COMPLETE RELIEF		PARTIAL RELIEF		SAME AS, OR WORSE THAN, 4 YEARS BEFORE	
		NO. (DIAGNOSES)	% (DIAGNOSES)	NO. (DIAGNOSES)	% (DIAGNOSES)	NO. (DIAGNOSES)	% (DIAGNOSES)
Chronic nervous exhaustion	55	14	25	17	31	24	44
Pelvic inflammatory disease	29	13	45	10	34	6	21
Lumbar or sacral pathologic condition	53	10	19	23	43	20	38
Appendicitis	31	19	61	7	23	5	16
Ovarian cysts	12	7	58	4	33	1	9
Uterine myomas	36	18	50	6	17	12	33
Dysmenorrhea	30	13	43	9	30	8	27
Constipation	25	8	32	8	32	9	36
Retroversion	18	4	22	6	33	8	45
Cervicitis	18	12	67	1	5	5	28
Relaxation†	17	8	47	5	29	4	24
Carcinoma	4‡	3	75	0	0	1	25
Endometriosis	9	5	56	3	33	1	11
Indeterminate	16	5	31	5	31	6	38
All others	54	24	44	12	22	18	34
Total diagnoses	207	163	40	116	29	128	31
Actual number of patients	310						

\*Some patients received more than one diagnosis.

†Relaxation of structures supporting pelvic viscera.

‡Ten of the original 16 patients with carcinoma had died in the interval of four years.

## TREATMENT AND ITS RESULTS

In general, the treatment of pelvic pain conformed to accepted conservative standards. For example, pelvic inflammatory disease was treated usually by the use of pelvic heat and, less commonly, by surgical measures; chemotherapy was not employed to any great extent in 1936. According to indications, neoplasms were treated surgically or by radium and roentgen therapy. The management of patients with nervous exhaustion, constitutional inadequacy, or functional disorders was often most difficult. Painsstaking physical and laboratory examination made the diagnosis more certain and sympathetic attention to the patient's complaints was valuable in gaining her confidence. Such confidence placed in the physician enabled him to reassure the patient and to develop a constructive program for regaining nervous stability, without which such pain was not relieved.

No attempt was made to tabulate the exact treatment which the patients had received. As a form of treatment, however, surgery occupies an important place in the management of conditions associated with pelvic pain. Aside from necessary operative skill, the success of surgical measures is necessarily dependent on the acuity of the physician in determining whether a given operation should be performed. Ordinarily, pelvic surgical operation is performed to remove diseased tissue, or as a restorative plastic procedure, and is seldom employed primarily for relief of pain. A notable exception is presacral neurectomy which may be employed in cases of intractable dysmenorrhea. It is, of course, important to relieve pain and the statistics given in Table II reveal that

TABLE II. EFFECT OF SURGICAL PROCEDURES ON PAIN OF PATIENTS WHO MADE CERTAIN COMPLAINTS

COMPLAINT ON FOLLOW-UP	TOTAL PATIENTS FOLLOWED	PATIENTS SUBJECTED TO SURGICAL OPERATION						
		NUMBER	PAIN, AS REPORTED ON FOLLOW-UP					
			COMPLETE RELIEF		PARTIAL RELIEF		SAME AS, OR WORSE THAN, 4 YEARS BEFORE	
			NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Lower abdominal pain	193	99	58	59	19	19	22	22
Backache	54	6	4	66	1	17	1	17
Menstrual pain	29	14	8	57	4	29	2	14
Multiple complaints	34	12	7	58	3	25	2	17
Total	310	131	77	58	27	21	27	21

this was accomplished with reasonable frequency. Almost half of the patients studied underwent some surgical procedure. Comparatively few patients with backache, however, were subjected to surgical operation. This is a reversal, now generally accepted, of the formerly prevalent opinion that backache is almost always a symptom of pelvic disease. Because of its relative infrequency, probably surgical operations performed on patients who complained of backache should be ignored in this discussion. Omitting those with backache, therefore, it is evident



AM. J. OBST. & GYNEC. 34: 1, 1937. (7) *Learmonth, J. R.*: Brain 54: 147, 1931. (8) *Lennander, K. G.*: Observations on the Sensibility of the Abdominal Cavity (translated by A. E. Baker), London, 1903, J. Bale, Sons & Danielsson. (9) *Lewis, T., and Kellgren, J. H.*: Clin. Sc. 4: 47, 1939. (10) *Mackenzie, James*: Brain 16: 321, 1893. (11) *Mackenzie, James*: Symptoms and Their Interpretations, ed. 3, London, 1918, Shaw & Sons. (12) *Meigs, J. V.*: New England J. Med. 222: 187, 1940. (13) *Morley, John*: Abdominal Pain, New York, 1931, William Wood & Company. (14) *Morley, John*: Brit. M. J. 2: 1270, 1937. (15) *Mussey, R. D.*: AM. J. OBST. & GYNEC. 37: 729, 1939. (16) *Ross, James*: Brain 10: 333, 1888. (17) *Spiegel, E.*: Internat. Clin. 3: 140, 1938. (18) *White, J. C.*: The Autonomic Nervous System; Anatomy, Physiology, and Surgical Treatment, New York, 1935, The Macmillan Company, pp. 102-114. (19) *Wright, Sampson*: Applied Physiology, ed. 7, New York, 1940, Oxford University Press, pp. 33-50 and 171-239.

## DISCUSSION

DR. HOUSTON S. EVERETT, BALTIMORE, MD.—I shall pass over Dr. Mussey's treatment of the neurologic and physiologic causes of pain and shall confine my discussion to emphasizing a few points brought out in his clinical analyses. In the first place, it should be noted that in his table of diagnoses there are found to be 74.4 per cent of his patients who were suffering from gynecologic conditions which might have contributed to their pain, but there were 81.6 per cent in whom some possible cause other than a gynecologic one was found. The multiplicity of conditions occurring in many patients, as he has mentioned, accounts for the fact that these two figures add to more than 100 per cent. Dr. Mussey as a gynecologist is distinctly to be congratulated on finding a greater number of nongynecologic than gynecologic conditions. I am afraid that the surgical specialist in any field is often too prone to attribute a patient's symptoms to those organs with which his line of work is particularly concerned.

Another point that is worthy of emphasis is the appreciable percentage of patients (17.6 per cent) in whom he found the pain due to chronic nervous exhaustion. This group of patients, as his results have shown, always constitute the most difficult therapeutic problem so far as relief of pain is concerned. We may divide patients suffering from pelvic pain into three large groups: First, those who have easily demonstrable organic lesions which require surgical correction and in whom the pain seems to be definitely associated with these lesions and is usually relieved by their correction. On the opposite end of the scale we may place those patients in whom, after very careful studies, no definite organic lesions can be demonstrated. Most of these patients should probably be placed in the group referred to under various names, such as chronic nervous exhaustion, as used by Dr. Mussey, or functional psychoneurosis with tension state, as is more frequently used by the psychiatrists with whom I am familiar. In the first of these groups the outlook for the relief of pain is excellent. In the second it is very poor and in the experience of most of us, I believe, these patients are usually best treated by thorough diagnostic study so that they can be positively assured of the absence of organic disease, after which some type of psychiatric regime should be instituted. It is common experience that manipulative treatments, such as unnecessary surgery or cystoscopic treatments, are likely to have a harmful rather than a beneficial effect on such patients.

Probably the most difficult group of all is that in which the patients have some organic lesion which at first seems that it might account for the pain, but the correction of which fails to give relief. A later analysis of many of the members of this group will show that they should originally have been placed in the group of psychoneuroses, and treatment along these lines eventually has to be instituted before any success is achieved.

I was a bit disappointed at the failure to find in Dr. Mussey's table of diagnoses any mention of disease of the urinary tract. Many urologists dealing particularly with the female, to mention only Hunner and William E. Stevens as outstanding examples, have given much emphasis, perhaps undue emphasis, to the urinary tract as a contributory factor in many types of pelvic and other pain. Even though their emphasis may be somewhat exaggerated an examination of the urinary tract should certainly not be omitted in the search for the cause of pain in a patient in whom it seems obscure. From my own experience, I am quite positive that no group of

treated medically (66 per cent). The greater efficacy of surgical measures is understandable because such measures are chosen in those definite conditions in which it is almost always possible to remove or correct the condition which is causing the pain. Nonsurgical treatment, on the other hand, must necessarily be employed in a larger percentage of instances wherein the diagnosis is indeterminate or the cause of the pain is functional rather than organic.

#### RELIEF OF PAIN IN RELATION TO DIAGNOSIS

It was obviously impossible to tabulate each of the many diagnoses; nevertheless Table IV is concerned with relief of pain according to some of the various diagnoses. As might be anticipated, a survey of this table shows that those patients who were nervously exhausted obtained the least benefit; nearly half of them stated that their pain was the same as it had been four years before, or worse. The observation that carcinoma almost never causes pain until it is in an advanced stage is supported by the known death of 10 of the original 16 patients with carcinoma in the interval of four years; 3 of the 4 known survivors stated that they had no pain.

#### SUMMARY AND CONCLUSIONS

Pain from the pelvic viscera reaches the consciousness of the individual through somatic afferent nerve fibers, called the "viscerosensory nerves," which pass upward from the pelvic viscera in the sympathetic chains; these nerves pass into cell stations at their proper level in the spinal cord where the stimuli are integrated or sorted out. The meager number and size of viscerosensory nerves, no doubt, account for the vagueness of localization of pain by the average individual unless the lesion affects also the parietal peritoneum which is more richly supplied by somatic nerves. When the normal selective function of the cell stations in the cord is weakened by vitiating disease or nervous exhaustion, many stimuli which would ordinarily be submerged reach the consciousness of the individual as pain.

When a reasonably accurate diagnosis is made of pelvic lesions which cause pain and which are amenable to surgical measures complete or partial relief of pain may be expected in 79 per cent of cases, depending on the condition and the nature of the operation.

Nonsurgical lesions or pain for which organic cause is not found, may be relieved in not more than 66 per cent of cases; in this group fall a considerable number of patients, about a fourth of all patients who complain of pelvic pain, who have no demonstrable organic lesion or who suffer from varying degrees of chronic nervous exhaustion. The scientific integrity of the physician is best maintained by his explaining to this type of patient, who is difficult to satisfy and reassure the physiologic basis of her pain.

#### REFERENCES

- (1) Davis, A. A.: *Brit. M. J.* 2: 1, 1934. (2) Head, Henry: *Brain* 16: 1, 1893.
- (3) Kinsella, F. J.: *Brit. J. Surg.* 27: 449, 1940. (4) Kinsella, F. J.: *M. J. Australia* 1: 681, 1940. (5) Kuntz, Albert: *The Autonomic Nervous System*, Philadelphia, 1929, Lea & Febiger, pp. 399-431. (6) Labate, J. S., and Reynolds, S. R. M.:

## A CRITICAL ANALYSIS OF BLOOD LOSS IN 2,000 OBSTETRIC CASES\*

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**D**URING the past ten years it has been agreed<sup>1, 2, 4, 6-8, 11-16, 18</sup> that the factors which contribute to increased blood loss are: increase in the weight of the mother, of the baby, and of the placenta, increased length of labor, general anesthesia, forceps delivery, laceration of perineum or episiotomy and last, mismanagement of the third stage.

The incidence of post-partum hemorrhage is given variously from 0.74 per cent (Smith<sup>3</sup>) to Peekham's figure<sup>4</sup> of 6.14 per cent and Pastore's<sup>10</sup> figure of 6.4 per cent, and the basic volume is expressed as from 500 to 600 c.c. or as Pastore<sup>11</sup> argues over 1 per cent of maternal body weight. Dieckmann and Daily<sup>7</sup> consider forceps delivery with episiotomy adds 235 c.c. to the volume lost through spontaneous delivery, while Calkins says episiotomy adds 60 c.c., a large baby adds 100 c.c., and mismanagement of the third stage adds 200 to 400 c.c. to the average blood loss.

The Dickinson-Pomeroy technique of third stage management is advocated by Smith<sup>3</sup> and Brandt.<sup>5</sup> Pastore and Stander<sup>16</sup> recommend the use of Calkins' principle of recognition of placental separation and advise the Pastore modification of the method of expression whereby the placenta is not used as a piston but is kept up out of the pelvis.

The routine injection of pituitrin intramuscularly is advocated by many men either before or after the placenta is delivered. Doerr<sup>9</sup> advises its use intravenously as do Dorset<sup>13</sup> and Peekham.<sup>4</sup> Many others employ the newer ergonovine intramuscularly (Smith<sup>17</sup>) or, as Davis<sup>18</sup> avers, intravenously even at the onset of the third stage.

Most men agree that, if necessary, manual removal of the placenta should be performed and the uterine cavity packed although Cosgrove<sup>19</sup> is definitely opposed to this latter procedure.

The blood loss should be replaced by glucose saline intravenously and (or) transfusion of blood. This, says Pastore,<sup>10</sup> will tend to minimize puerperal infection and decrease hospital stay.

For some time we have been amazed to note a greater measured blood loss following delivery than we had judged there would be. With this in mind we feel that a review of a series of consecutive deliveries would be justified since it would enable us to determine the average blood loss, the incidence of post-partum hemorrhage (i.e. 600 c.c. or more), the factors which contribute to the increase, the causes, and prophylactic measures to prevent this grave complication. That increased blood loss is a grave complication is proved by the records of the Province of Alberta for the years 1936 to 1939, inclusive. Dur-

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500 women suffering from pelvic pain could be found in which there would not be discovered a substantial number of urinary tract lesions if they were looked for.

In order to determine the possible effect on the urinary tract of various gynecologic conditions one of my associates and I recently have made complete urologic studies on a series of 100 patients. We found varying degrees of dilatation of the ureters and pelvis in 50 per cent of these. After appropriate treatment of their gynecologic conditions about 30 of the 50 patients who originally showed dilatation have been subjected to restudy. In about half of these the urinary tracts had failed to return to normal although in some instances, a number of months had elapsed since the completion of their gynecologic treatment. It occurred to me that this finding might throw some light upon the occasional failure completely to relieve pain by the appropriate surgical correction of some gynecologic lesions.\*<sup>15</sup>

DR. MUSSEY (Closing).—I am glad that Dr. Everett emphasized the group of patients with pelvic pain who have organic trouble and also psychoneurosis. Observation of women with pelvic pain has demonstrated that one must be guarded in promising complete relief of complaints, and particularly of pain, to patients who have conditions which require operation. In reference to lesions of the urinary tract, I may say that these were included under the heading "multiple complaints."

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\*Percentages given in this discussion are based on the following article: *Mussey, R. D.: AM. J. OBST. & GYNEC. 37: 729, 1939.*

TABLE II. WEIGHT OF BABY AND BLOOD LOSS

WT. IN GRAMS	PRIMIPARA		MULTIPARA		TOTAL		P.P. HEMORRHAGE	
	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS
Under 2,500	46	283	60	158	106	221	10	720
2,500-2,999	136	304	184	234	320	264	29	775
3,000-3,499	370	375	463	246	833	303	117	813
3,500-4,000	197	475	351	303	548	365	110	848
Over 4,000	39	469	127	383	166	403	41	897
Twins	12	562	15	502	27	529	7	997
	800		1,200		2,000		314	

TABLE III. WEIGHT OF PLACENTA AND BLOOD LOSS

WT. IN GRAMS	PRIMIPARA		MULTIPARA		TOTAL		P.P. HEMORRHAGE	
	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS
Under 453	36	278	44	245	80	260	6	757
454-567	346	358	476	251	822	296	111	812
568-680	266	397	394	274	660	323	97	847
681-793	101	465	178	325	279	375	63	815
794-907	27	403	65	341	92	359	17	835
908-1,134	21	577	34	426	55	484	17	957
Over 1,134	3	400	9	397	12	399	3	870
	800		1,200		2,000		314	

ages between 453 Gm. and 680 Gm. The smaller blood loss where the placenta weighed over 1,134 grams is probably not consistent with that which would accrue in a large number of such cases. This, as others have pointed out, suggests that the amount of blood loss is proportionate to the amount of retraction of the uterus which is necessary following delivery.

TABLE IV. DURATION OF LABOR AND BLOOD LOSS

DURATION	PRIMIPARA		MULTIPARA		TOTAL		P.P. HEMORRHAGE	
	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS
Under 3 hr.	25	231	201	259	226	256	29	770
3-10 hr.	296	377	649	285	945	314	135	840
10-20 hr.	333	371	269	290	602	335	99	806
20-30 hr.	101	475	66	264	167	391	37	868
Over 30 hr.	45	480	15	248	60	422	14	907
	800		1,200		2,000		314	

Table IV shows a progressive increase in blood loss varying directly with the duration of the labor. The average duration in primiparas was calculated as fourteen hours, that in multiparas as nine hours; the total average as 10.5 hours. The increased average in primiparas was due to several factors: almost 60 per cent were in labor more than 10.5 hours as compared to 29 per cent of the multiparas. This increased length of labor leads to an increased amount of sedation as a rule, an increase in operative delivery, and greater fatigue of the mother.

The method of delivery in its relation to blood loss is shown in Table V. Of the 2,000 cases, 66 per cent delivered spontaneously with an average blood loss of 278 c.e. With low forceps delivery (24 per cent), the average blood loss was increased 126 c.e. Midforceps delivery further increased the blood loss as might be expected. In breech de-

ing this period, 64,607 deliveries were recorded. In this group there were 161 maternal deaths, and of this number, 49, or 30 per cent, were considered due to post-partum hemorrhage, a figure which surpasses Cosgrove's<sup>19</sup> recorded incidence of 25 per cent. No records are available of the number of mothers whose puerperium has been prolonged or who have become chronic invalids directly or indirectly as a result of excessive blood loss, which has been recognized too late, or not at all, by the attending physician. And indeed he is unlikely to appreciate the significance of excessive blood loss during the third stage unless he is keenly interested and has a simple but relatively accurate method of measurement.

There are very few hospitals in Canada where any attempt is made to measure blood loss. Some, it is true, try to estimate the volume, but it is obvious that this is markedly inaccurate and, indeed, sometimes misleading. Sad to relate, a few make no attempt at even an estimation. Since we cannot find any published record from any Canadian hospital obstetric service, it is hoped that this review will stimulate interest and provide the impetus for further investigation of this problem throughout the Dominion.

Our apparatus for measuring blood loss is cheaply made, easily attached to any table and is relatively accurate. Amniotic fluid which collects following rupture of the membranes can be easily dumped, and the amount of "after waters" in the pan usually balances the amount of blood which collects on the linen.

Our series comprises 2,000 consecutive vaginal deliveries up to Dec. 31, 1940, of which 800 were primigravidas, and 1,200 were multiparas. We have made no attempt to classify them further. The average blood loss for all primiparas was 388 c.c., for multiparas it was 280 c.c., and for the series averaged 323 c.c. As before stated, this is higher than we expected.

TABLE I. WEIGHT OF PATIENT AND BLOOD LOSS

WEIGHT (POUNDS)	PRIMIPARA		MULTIPARA		TOTAL		P.P. HEMORRHAGE	
	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS
Under 120	20	266	17	321	37	291	2	775
121-140	247	382	359	278	607	320	94	840
141-160	391	384	436	263	927	314	140	785
161-180	111	405	213	310	324	343	58	912
181-200	25	482	49	255	74	332	12	899
Over 201	5	516	26	403	31	421	8	886
	800		1,200		2,000		314	

Table I shows the relation between weight of the patient and blood loss. It is evident that the increase in average blood loss corresponds to the increase in the mother's weight. This same tendency is also apparent in the group whose blood loss is 600 c.c. or more. In Table II there is a similar increase following the delivery of a large baby or of twins.

In Table III the same holds true; in the main the increased weight of the placenta is more likely to result in increased blood loss, although in approximately 75 per cent of the cases, the placental weight aver-

a small vagina, a combination which is relatively common in our experience, and which merits our constant attention. A just criticism might be made that we did not iron out the lower vagina and perineum, but this has happened in spite of the fact that the ironing out was done, and moreover that the perineum was infiltrated with local anesthesia. We feel that this accident cannot be avoided in a certain number of cases. Local infiltration of the perineum in our experience decreases the local blood loss and lessens the amount of general anesthesia, thereby minimizing uterine atony. It does, however, to a large extent abolish the "perineal urge" and so increases the use of outlet forceps application.

TABLE VII. DURATION OF THIRD STAGE AND BLOOD LOSS

DURATION	PRIMIPARA		MULTIPARA		TOTAL		P.P. HEMORRHAGE	
	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS
Under 6 min.	176	378	323	245	499	292	69	798
6-15 min.	466	366	757	279	1,223	312	169	828
16-30 min.	139	450	109	369	248	415	68	836
31-60 min.	14	474	10	380	24	438	6	967
Over 60 min.	5	625	1	50	6	529	2	1,112
	800		1,200		2,000		314	

The average duration of the third stage was thirteen minutes. There was, as shown in Table VII, a progressively increasing blood loss as the duration of the third stage was prolonged. This is very noticeable in that group (15 per cent) where the third stage was longer than fifteen minutes. This is due probably to atony of the uterus, to partial separation of the placenta, or to tardy recognition of complete separation. In this table, the blood loss in primiparas averaged 100 c.c. more than in multiparas, and is due most likely to the extra blood loss from a larger laceration or episiotomy. However, the conduct of the third stage does play a part in the blood loss. Early recognition of placental separation is essential whether by the criteria of Calkins, or by individual modification. We do not believe that the placenta should be expressed after the first uterine contraction, but rather that the uterus should rise in the abdomen, should become globular, firm, against the anterior abdominal wall and be freely mobile. This may need more than one contraction but is usually indicated by slight uterine bleeding. We have found Pastore's method of expressing the placenta ideal for most cases except where the abdominal wall is thick and resistant, when it then is difficult. However, if the uterus is pushed into the pelvis we believe it should be elevated immediately after the placenta is out even if combined abdominal and vaginal pressure is necessary. At this stage, early in the series, ergonovine 0.2 mg. (ergotrate, Lilly) was injected intramuscularly, but we soon found that a quicker response could be obtained by injecting the alkaloid immediately after the birth of the baby, with no greater tendency to contraction of the cervix, and incarceration of the placenta. Lately we have been injecting ergotrate intravenously as soon as the baby is born. This has speeded up placental separation markedly and to date has yielded no untoward results, although the increased possibility of contraction of the cervix with incarceration of the placenta must be recognized.

Uterine tamponade was employed in 24 instances. Where, in spite of massage and medication, we are unable to keep the uterus elevated and

TABLE V. METHOD OF DELIVERY AND BLOOD LOSS

METHOD	PRIMIPARA		MULTIPARA		TOTAL		P.P. HEMORRHAGE	
	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS
Spont.	371	323	965	261	1,336	278	156	812
Low Forceps	314	429	162	356	476	404	112	828
Midforceps	19	541	8	362	27	488	7	923
Forceps Rot.								
Midforceps	26	551	12	245	38	454	10	837
Manual Rot.								
Midforceps	24	491	10	488	34	490	11	932
Breech	34	385	25	247	59	327	9	863
Twins	10	477	14	502	24	492	7	963
Inc. of Cerv.	1	1,225	0	0	1	1,225	1	1,225
Version and extraction	1	200	4	429	5	383	1	660
	800		1,200		2,000		314	

livery and version and extraction, the blood loss surprisingly was lower than in low forceps delivery. While the number of cases is smaller, yet the incidence of breech presentation (3 per cent) conforms to the accepted figure. We employ version and extraction rarely, which explains the small number of cases. It is possible a larger number would result in a relatively greater blood loss.

TABLE VI. STATE OF PERINEUM AND BLOOD LOSS

	PRIMIPARA		MULTIPARA		TOTAL		P.P. HEMORRHAGE	
	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS
Intact	65	189	564	206	629	206	39	786
Lac. 1st Deg.	71	266	300	288	371	284	44	812
Lac. 2nd Deg.	20	365	29	343	49	352	10	849
Lac. 3rd Deg.	4	425	1	550	5	450	1	600
Episiotomy	613	397	306	396	919	395	195	828
Episiotomy and side wall tear	27	980	0	0	27	980	25	1,019
	800		1,200		2,000		314	

Table VI demonstrates the increasing average blood loss where the perineum was torn or incised. In 32 per cent of all cases the perineum was intact, and the average blood loss was 206 c.c. Even a slight laceration (19 per cent) resulted in an average increase of 78 c.c. A second degree laceration resulted in a further increase of 136 c.c., while in the 5 cases wherein a third degree laceration occurred, the blood loss more than doubled that from an intact perineum. Our practice of performing episiotomy is quite evident from the table. Seventy-seven per cent of primiparas and 25 per cent of multiparas were so treated with an average blood loss of 395 c.c., an increase of 189 c.c. over the loss through the intact perineum. This increase is more than we expected, so much so, that we are considering a change or at least a modification of this procedure. In 27 cases there occurred an extension of the episiotomy upward along one or both lateral walls of the vagina. These lacerations bleed profusely, are difficult to repair, and explain the average blood loss of 980 c.c., a truly alarming amount! These accidents are not all due to inexperienced forceps application, or traction, but are usually associated with a narrow pelvic outlet, a long sacrum, and



TABLE VIII. SEDATIVES AND BLOOD LOSS

SEDATIVE	PRIMIPARA		MULTIPARA		TOTAL		P.P. HEMORRHAGE	
	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS	NO.	AV. BL. LOSS
No sedative	10	251	53	266	63	264	8	780
Nembutal alone	67	306	242	229	309	246	30	806
Nembutal and paraldehyde	460	406	683	288	1,143	335	191	854
Nembutal, paraldehyde and ether	66	432	74	175	140	295	27	786
Other combinations	197	365	148	309	345	341	58	773
	800		1,200		2,000		314	

mild somnolence is preferable to unconsciousness, and moreover the peak should be reached during late first stage. During the expulsive stage, the patient can be aided by intermittent gas anesthesia together with local perineal infiltration, thereby decreasing the tendency to atony of the uterus during the third stage.

TABLE IX. BLOOD LOSS IN 100 C.C. GROUPS

AMOUNT IN C.C.	PRIMIPARA	MULTIPARA	TOTAL	%
0-100	107	400	507	25.3
101-200	158	263	421	21.1
201-300	155	169	324	16.2
301-400	80	113	193	9.6
401-500	92	86	178	8.9
501-600	38	25	63	3.2
601-700	67	59	126	6.3
701-800	29	25	54	2.7
801-900	28	23	51	2.5
901-1,000	16	16	32	1.6
1,001-1,500	27	17	44	2.2
1,501-2,100	3	4	7	0.4
Average — 323	800	1,200	2,000	100.0

Table IX and Fig. 1 show an analysis of blood loss in 100 c.c. groups. Sixty-two and five-tenths per cent of all cases show a loss of 300 c.c. or less. The incidence then drops sharply and continues in a gradual slope except for a slight rise in the 600 to 700 c.c. group.

Of the 800 primiparas, 170, or 21 per cent, had blood loss of 600 c.c. or more, as did 144, or 12 per cent, of the 1,200 multiparas. Thus 16 per cent of the total 2,000 patients had post-partum hemorrhage, a much higher incidence than is reported in the literature. On the other hand, if we take into consideration the percentage blood loss rather than the actual volume loss, we find the incidence in primiparas is 14.4 per cent, in multiparas 7.4 per cent, with a total incidence of 10 per cent, a figure much lower and relatively comparable. We agree with Pastore<sup>16</sup> that this is a more reasonable basis on which to grade blood loss and moreover, if agreed upon, will provide a basis of comparison for further investigations.

Closer analysis reveals that the patients with blood loss in excess of 600 c.c. bear practically the same relation to the various factors given in Tables I to VIII as do the total series. What then causes this great increase in total blood loss? In order to examine the problem we pursued our investigation along two channels: first, we carefully reviewed

well contracted, or where vaginal wall oozing persists, we do not hesitate to pack the uterine cavity. For this we use a homemade instrument, a sigmoidoscope 2 cm. in diameter whose obturator has been converted into a trident. The tube is inserted into the uterine cavity and 2 inch dry gauze is pushed through the lumen as far as desired. The packer is gradually removed and the vagina in turn is packed, 3 to 6 yards of gauze in all being used. This keeps the uterus elevated, effectively controls oozing and may be removed twelve to twenty-four hours later. In our experience there has been no relative increase in morbidity where packing has been inserted and, where all other measures seem to fail, we find it a valuable asset.

It would be ideal for every woman whose blood loss is 600 c.c. or more to have a blood transfusion immediately, but from a practical point of view, some of them do not seem to require it. The reaction to blood loss varies according to size and weight, and this must be taken into consideration. In some patients the restoration of fluid volume by intravenous glucose is sufficient—in others this must be supplemented by blood transfusion. This restoration of blood volume undoubtedly reduces morbidity and mortality during the puerperium.

A greater interest in the technique of the third stage leads to a closer observation of the mechanism and quicker attention to and treatment of any variation, thereby decreasing the blood loss. We have experienced this ourselves since we commenced the present review.

In previous articles<sup>20, 21</sup> we stated that the blood loss as a result of giving sedation to secure amnesia and analgesia was not materially increased. We admit that our analysis of blood loss was based on a smaller series of cases than the present, and moreover was not as definitely linked up with the various other factors which might influence the volume. In the light of this analysis, our opinion should perhaps be modified in some degree.

We have tried several combinations of drugs, as in Table VIII with varying results. Three hundred and seventy-two patients, or 19 per cent, received no sedative or else nembutal alone, with an average blood loss of 249 c.c. Practically all of these cases were labors of short duration in which the need for sedation was not great. The largest group, 57 per cent, were given nembutal by mouth and paraldehyde either by mouth or per rectum; here the blood loss was increased to 335 c.c. This increase is most marked in the primipara (450 c.c.) but may be due to the large number of episiotomies. A smaller series (7 per cent) received nembutal by mouth and a mixture of paraldehyde and ether per rectum. The resulting average blood loss was increased in primiparas, but decreased in multiparas with a total average of 295 c.c. In the last group in Table VIII where various combinations of drugs were tried (these included nembutal, morphine, heroin, hyoscine, atropine, paraldehyde, and ether) the blood loss was highest. All these cases had long labors due to relative disproportion, soft tissue dystocia, or ineffective labor pains, and consequently resulted in an increased incidence of operative delivery. All these factors were contributory to the increase.

We still believe that sedation has a definite place in the conduct of labor, but our experience has led us to modify our procedure over the course of the years. We have decreased the dosage considerably and changed the time of administration. We believe that comfort or

enlarging the wound and repairing the relaxed perineum at this time as it definitely contributes to increased bleeding.

In 60 cases, instrumental delivery was judged to be the cause. Twenty-eight were delivered by midforceps application; of these, 21 were arrested occipitoposterior positions, while the remainder were anterior positions which were "tight fits." Associated with forceps delivery in 24 cases was a side wall tear which bled profusely. Low forceps delivery accounted for 32 cases; it would appear that even this operation is not without danger. Perhaps in some instances we might have waited a little longer before resorting to forceps application. A continuing review of our records will no doubt provide the answer.

In 56 cases there seemed to be no obvious reason for the excessive blood loss. In 12 of these, delivery was spontaneous through an intact perineum. The remainder were spontaneous or low forceps delivery, with episiotomy or lacerated perineum. While all the factors previously mentioned were undoubtedly in evidence, it is possible that faulty recording at the time of delivery may have been responsible for our inability to ferret out a single cause for the hemorrhage.

Uterine atony alone or with other lesser causes accounted for 41 cases. Some of these were due to mismanagement of the third stage, others were unaccountable. This might apply to any series.

In 32 cases, sedatives were, we felt, the primary cause. In many instances the total dosage was relatively too great, in others sedative was given too near the time of actual delivery. In the latter instance especially, the result was arrest on the perineum, with a greater incidence of forceps delivery, longer general anesthesia, and atony following delivery. The desirability of having the sedative wear off as delivery approaches, so that the patient may "bear down" to effect spontaneous birth, is evident.

TABLE XI. REASONS FOR POST-PARTUM HEMORRHAGE

CAUSE	PRIMIPARA	MULTIPARA	TOTAL
Twins, large babies, breech	11	9	20
Long labor	15	4	19
Precipitate labor	1	9	10
Premature separation of placenta	1	4	5
Retained placenta	3	1	4
			58

In Table XI the less common causes are noted. In 20 cases the delivery of twins or a large baby was cited as the cause. Associated was a large placenta and the need for greater uterine retraction was quite evident.

Long labor was the cause in 19 cases. Here the usual results of maternal fatigue with operative delivery and atony of the uterus are in evidence. On the other hand, 10 patients were delivered precipitately with resulting hemorrhage. The need for immediate uterine stimulation (probably intravenous ergotrate) is indicated in this complication.

Premature separation occurred as a cause on 5 occasions. An increased loss cannot be obviated in some instances where this complication arises.

each hemorrhage case record to find out the several causes or, if possible, the single cause and; second, we planned the study of a series of 150 unselected deliveries on which blood was taken shortly before delivery and during the puerperium with a view to determine blood dilution and recovery consequent to third stage blood loss.

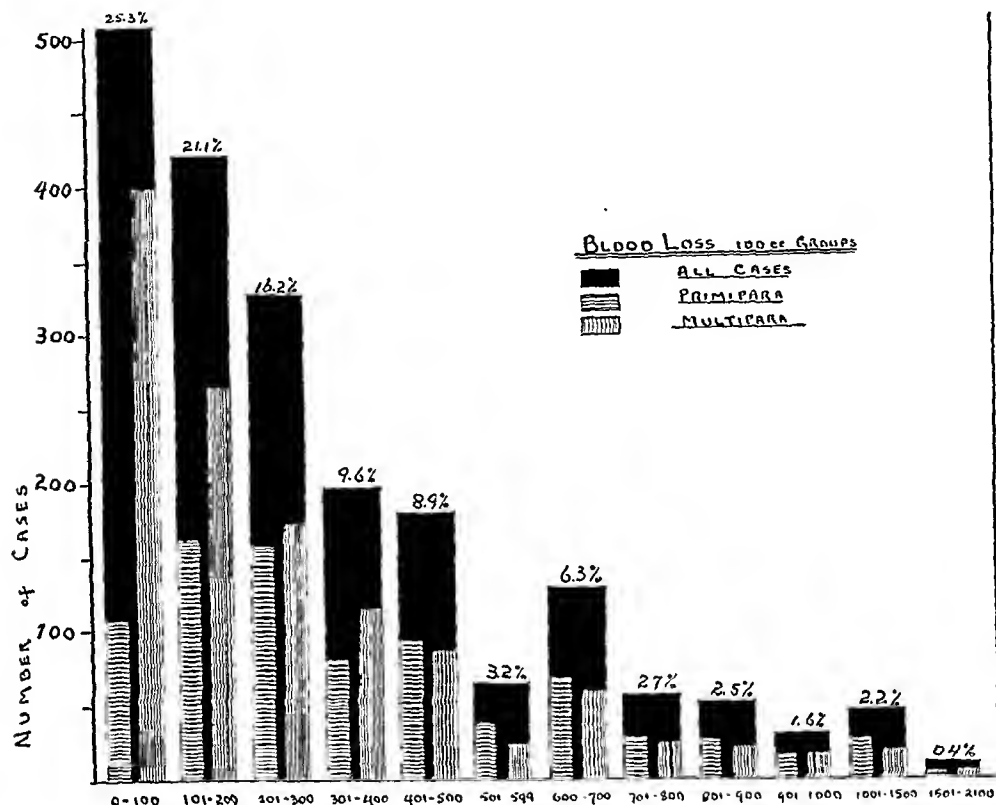


Fig. 1.

In Table X are shown the more common single causes of hemorrhage, of these the largest number (67) are associated with episiotomy, laceration, or repair of a relaxed perineum.

TABLE X. REASONS FOR POST-PARTUM HEMORRHAGE

CAUSE	PRIMIPARA	MULTIPARA	TOTAL
Episiotomy laceration or repair	33	34	67
Instrumental delivery	51	9	60
No reason	26	30	56
Uterine atony	13	28	41
Sedative	16	16	32
			256

Since, of the 314 cases in the hemorrhage group, 126 with perineal wounds lost between 600 and 700 c.c., it is reasonable to suppose that the bleeding from the wound was of itself sufficient to cause their inclusion. This bears out our previous statement and makes us wonder if our very frequent use of incision is always justified. Even with a laceration of the perineum there is but little decrease in the blood loss while the jagged wound is more difficult to repair. We do not advise

this procedure relatively simple and accurate. Serum was used to avoid errors introduced by an anticoagulant and by hemolysis. In order to balance the study, estimations of hemoglobin, red blood cells, and packed red cells were carried out on whole blood collected at the same time. Blood loss was measured as described and calculated on the basis of percentage of body weight before delivery. Proteins in serum were calculated from the specific gravity according to formula of Weech and others,<sup>25</sup> many results being checked by nitrogen determinations. The results obtained were tabulated according to blood loss in percentage of admission weight and are given in Table XII.

TABLE XII. RELATION OF BLOOD LOSS TO HEMOGLOBIN AND RED CELLS

BLOOD LOSS PER CENT OF WEIGHT ON AD- MISSION	HEMOGLOBIN SAHLI GM./100 C.C.			RED BLOOD CELLS MILLIONS/C.MM.			PACKED RED CELLS PER 100 C.C. WHOLE BLOOD		
	1	2	3	1	2	3	1	2	3
0.1	11.7	11.7	13.5	3.83	3.71	4.22	39.6	41.2	46.5
0.24	11.7	11.6	13.3	3.89	3.71	4.21	41.8	40.6	46.1
0.38	11.7	11.7	12.8	3.67	3.67	4.08	40.0	39.8	45.0
0.55	12.1	11.9	12.3	3.79	3.82	4.20	40.0	38.6	46.2
0.63	12.3	11.8	12.2	3.96	3.72	4.03	41.0	38.7	42.6
0.80	11.2	10.5	11.1	3.73	3.45	3.74	39.8	37.3	40.7
0.97	10.1	10.2	11.5	3.63	3.41	3.80	38.6	35.0	41.4
1.06	11.6	9.2	9.9	3.91	3.21	3.62	36.0	30.6	35.5
1.10	10.4	9.0	10.1	3.45	3.26	3.44	39.6	32.6	38.6
1.53	11.6	9.9	10.7	3.83	3.33	3.54	41.3	32.8	38.3

This study is limited to conditions just prior to delivery, twenty-four hours after delivery and on the tenth post-partum day, indicated in the table as 1, 2, and 3. Studies during pregnancy are in progress and will be dealt with in a separate communication.

It will be seen that values for hemoglobin, red blood cells, and packed red cells in the ante-partum specimen bear no definite relationship to the blood loss, apart from being consistently low. Values on the first post-partum day are consistently lower than those of the initial specimen, the difference being most marked where the blood loss exceeds 1 per cent of the body weight. This is best illustrated in the case of the packed cell volume calculated for the third post-partum day, and our findings agree substantially with those of Pastore. Values on the tenth post-partum day indicate the degree of recovery in each group. It will be seen that where the blood loss did not exceed 0.5 per cent of the body weight (approximately 400 c.c.), recovery was complete. If it was in excess of that amount, then the degree of recovery roughly paralleled the blood loss, lesser recovery being related to greater blood loss. That this is not absolute is indicated by the crossed lines in Fig. 2, where, for example, recovery from blood loss of 0.55 per cent of body weight is greater than that from 0.24 per cent, and that from 0.97 per cent is greater than that from 0.63 per cent. The values of the first post-partum day seem much more significant and consistent for that correlation. However, since the absolute differences are so small, it does not seem reasonable to put too great emphasis on these values, except in those cases where the blood loss exceeds 1 per cent of the body weight.

In 4 cases the hemorrhage was due to retained placenta; efforts to express it failed. Accordingly, in each case, manual removal was employed.

In this total series there were 30 cases where the third stage lasted longer than thirty minutes but only in 7 was the placenta removed manually. We advise manual removal only when there is profuse or persistent uterine bleeding, where the uterus does not respond to stimulation and where efforts to express the placenta fail. In one case indeed where a thick contraction ring foiled attempts at manual removal, the placenta was left in place. Pelvic examination at six weeks post partum showed a well-involved uterus; the placenta had apparently become completely absorbed. At no time had there been much bleeding.

Even with the increased blood loss, recovery was in the main uneventful. There were no maternal deaths from post-partum hemorrhage, either at delivery or during puerperium. The general morbidity rate (100.4° F. or over) was 9.6 per cent, while in the hemorrhage group the uncorrected rate was 12.7 per cent. Eighty per cent of these latter patients left the hospital by the twelfth day post partum, while only 7 per cent remained longer than fourteen days.

At the postnatal examination, blood counts in 150 cases were compared with those taken at the first prenatal examination. In 90 per cent the counts were equal to or better than those made at the initial visit. The red cell count averaged 3,900,000 and the hemoglobin estimation averaged 12.5 Gm. per cent.

These are the results of our first avenue of investigation.

Our second avenue, dealing with blood dilution and recovery consequent to blood loss, requires a brief introduction:

Pastore<sup>22</sup> studied the packed red cell volume before delivery and during the puerperium and showed that the cell volume on the third post-partum day varied with the blood loss expressed in terms of percentage of body weight. Using this latter value, he presented data from which the packed cell volume on the third day could be calculated. On this calculation he then based the events which might be expected during the puerperium.

It is now definitely agreed that following an acute hemorrhage, compensation for the decreased blood volume is effected by blood dilution. Plass and Bogert,<sup>23</sup> Stander and his associates,<sup>24</sup> and many others have shown that there is blood dilution during pregnancy. Further dilution consequent to blood loss must then occur immediately following delivery. That compensation for dilution occurs after delivery in many cases is indicated from Pastore's studies, but studies on blood dilution due to blood loss during the third stage of labor seem to be lacking. While such effects might be indicated by red cell volume studies, we felt that these would not give absolute results, since diluted plasma, due to its hypotonicity might affect the size of the cells and as a result the cell volume.

It is now well established that hemorrhage is followed by a decline in the specific gravity of the blood. Since this is due mainly to plasma dilution, it seemed pertinent to examine the specific gravity of the blood serum at certain periods before labor and during the puerperium. Recent developments in methods of estimating specific gravity make

TABLE XIII. RELATION OF BLOOD LOSS TO BLOOD DILUTION

BLOOD LOSS PER CENT OF WEIGHT ON AD- MISSION	PACKED RED CELLS IN PER CENT OF ADMISSION SPECIMEN/100%			SERUM SPECIFIC GRAVITY			SERUM PROTEINS GM./100 C.C.		
	2	*	3	1	2	3	1	2	3
0.1	104	105	117	1.0238	1.0225	1.0276	5.75	5.31	7.04
0.24	97	102	110	234	222	263	5.60	5.12	6.58
0.38	99	98	112	239	222	262	5.78	5.12	6.57
0.55	96	92	115	238	229	268	5.74	5.43	6.78
0.63	94	89	103	234	219	254	5.60	5.12	6.33
0.80	93	84	102	223	218	253	5.22	5.07	6.28
0.97	90	85	107	227	213	252	5.38	4.47	6.24
1.06	85	84	98	228	205	249	5.41	4.59	6.13
1.10	82	82	97	222	192	231	5.12	4.14	5.51
1.53	79	70	92	206	187	236	4.62	4.00	5.67

\*Calculated for third post-partum day, after Pastore.\*\*

fleeted quite accurately the blood dilution consequent to it. The tenth day values indicated the degree of recovery. This is illustrated in Fig. 3 where values in excess of 1.0260 indicate complete recovery and represent all cases in which the blood loss did not exceed 0.5 per cent of the body weight.

#### SUMMARY

On the basis of our findings in 150 unselected cases which constituted this part of the study, we feel justified in suggesting that:

1. The specific gravity of the serum obtained within twenty-four hours prior to delivery is a rough index of the extent of blood loss in the third stage of labor. Values exceeding 1.0235 are associated with blood losses not exceeding 0.5 per cent of the body weight. Values in excess of 1.0230 correspond to blood loss not exceeding 1.0 per cent of the body weight. Values below 1.0230 indicate that blood loss in excess of 1.0 per cent of the body weight might be expected.

2. The specific gravity of the serum on the first post-partum day is an accurate index of the blood loss and reflects blood dilution due to blood loss.

3. The tenth day value is an index of the extent of recovery from dilution due to blood loss as well as dilution which occurred during pregnancy.

4. Since both hematocrit measurements and specific gravity estimations indicate that complete recovery from blood loss occurs within ten days of delivery, providing that the blood loss does not exceed 0.5 per cent of the body weight (approximately 400 e.e.) and since complete recovery does not take place in that period by these criteria when the loss exceeds that amount, then a blood loss in excess of 0.5 per cent of body weight should be considered post-partum hemorrhage and adequate treatment instituted.

#### CONCLUSIONS

We have presented an analysis of 2,000 cases of vaginal delivery with an average blood loss of 323 e.e. In 314 cases (15.7 per cent), there was blood loss of 600 e.e. or more, but only in 205 (10 per cent) was

Since the proteins were calculated from the specific gravity, it will suffice to discuss only the specific gravity. Table XIII summarizes our findings for these and correlates them with changes in the packed cell volume. It will be seen that the values in the specimens obtained

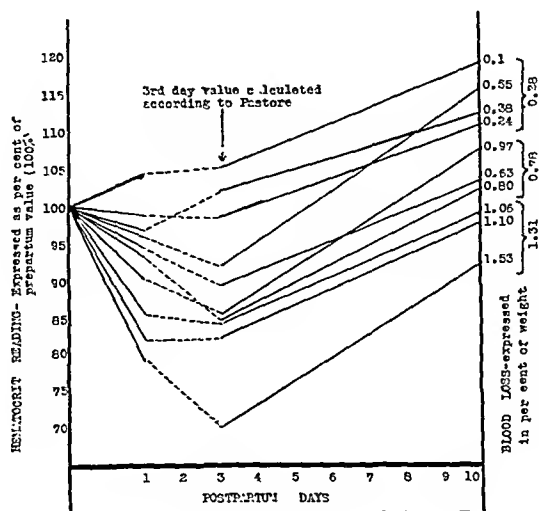


Fig. 2.

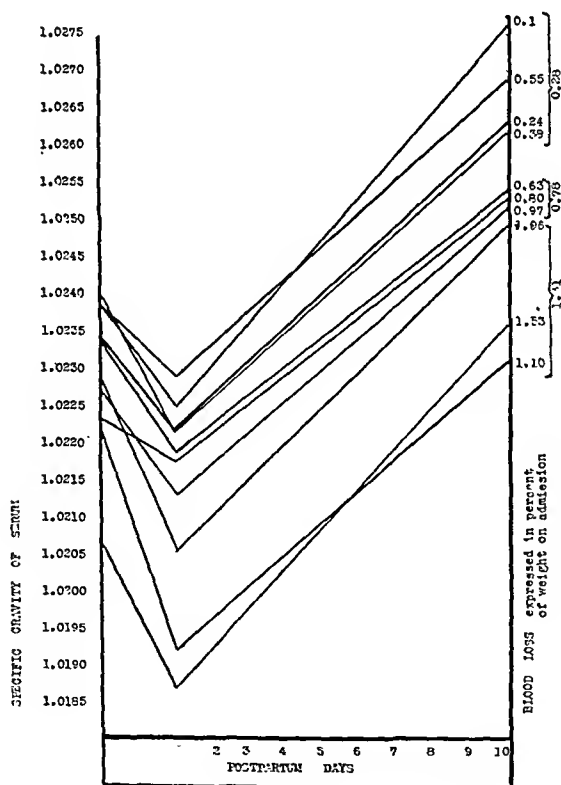


Fig. 3.

before delivery closely parallel the blood loss, and that all are well below the normal value (1.0260-1.0275). The lower the specific gravity, the greater was the subsequent blood loss. So too, the twenty-four-hour post-partum specimen closely paralleled the blood loss and re-



not suffer some blood loss, but the question is what is the natural blood loss, and what exceeds it? Dr. Dieckman and Dr. Daily found that on an average the normal blood loss was about 107 c.c., 342 c.c. for forceps operations, and 539 c.c. for cesarean sections.

We have been interested in controlling the blood loss of the third stage and the postpartum period.

We must consider first, however, the physiology or mechanism of the third stage which we believe has not been sufficiently recognized. I have always taught that the third stage consists of two phases. We have the idea that the mechanism of separation of the placenta is due largely to the change in volume of the body of the uterus and that the contraction of the placental segment of the uterus after the baby is expelled is what really effects the separation of the placenta. After the child is expelled naturally the size of the uterus is decreased very materially. It is not until the placental segment of the uterus begins to contract that the placenta separates from the uterine wall thus ending the first phase. By contractions of the uterus it is eventually expelled, completing the second phase of the third stage.

On the assumption that this theory is correct, we have been investigating the use of ergonovine during the third stage. After some trial we finally decided to give intravenous and intramuscular injections of ergonovine as the child was being delivered. We now await the delivery of the head and as the shoulders are being expelled we give an injection of ergonovine, 0.2 mg., as the size of the uterus diminishes with a contraction. This stimulates contractions of the segment under the placental site and facilitates or steps up the first phase, i.e., the separation of the placenta from this segment, so that by the time the child is delivered the separation of the placenta is practically complete and the stage of expulsion follows promptly.

TABLE I. POST-PARTUM HEMORRHAGE, 1,000 DELIVERIES (PRIMIPARAS)

BLOOD LOSS	NATURAL			OPERATIVE		
	2ND		3RD	2ND	3RD	
		IV	IM		IV	IM
500-600 c.c.	0	1	1	1	3	0
600-1,000	0	1	0	0	0	0
1,000-1,500	0	1	0	0	0	0

Table I shows the results in 1,000 consecutive primiparous deliveries both natural and artificial. The amount of blood loss is shown in the left-hand column; the time and the number of cases are shown in the other columns. The natural and operative deliveries are listed separately, and the second and third stages are shown. The method of administration is indicated as intravenous or intramuscular. A corresponding series of multiparous deliveries is shown in Table II.

TABLE II. POST-PARTUM HEMORRHAGE, 1,000 DELIVERIES (MULTIPARAS)

BLOOD LOSS	NATURAL			OPERATIVE		
	2ND	3RD		2ND	3RD	
		IV	IM		IV	IM
500-600 c.c.	0	3	5	0	3	2
600-1,000	0	6	0	0	0	0
1,000-1,500	0	1	0	0	0	0

It is important that the second phase be completed promptly. Otherwise a contracting lower segment may interfere with the expulsion of the placenta. If there is bleeding it is likely to be due to lacerations rather than atony. Occasionally also downward pressure of the uterus causes bleeding by kinking the large veins and producing marked venous stasis. As a rule the longer the second stage and the third stage the greater is the blood loss.

there a loss exceeding 1 per cent of body weight. Our data confirm the results already established, namely that increased blood loss is related to (1) increase in the weight of the mother, of the baby, and of the placenta; (2) prolongation of labor; (3) operative delivery; (4) laceration or incision of perineum; (5) prolongation of third stage; and (6) ill-judged sedation.

Our data indicate that the commoner causes for post-partum hemorrhage are instrumental delivery, uterine atony, and ill-judged sedation with, as contributory causes, a large baby or twins, long labor, premature separation, or retained placenta. In 56 cases no obvious cause could be attached. The factors concerned in post-partum hemorrhage conform essentially to those already enumerated for the whole group. We have also presented a small series of 150 cases wherein blood dilution as a factor in blood loss was studied. Our data suggest that the specific gravity of the serum obtained shortly before delivery may be used as a rough index of the extent of the blood loss in the third stage and may serve as a warning of an unexpected complication. Since recovery from blood loss judged by serum specific gravity values is complete within ten days, providing the loss does not exceed 0.5 per cent of the body weight (approximately 400 c.c.), it is suggested that any loss in excess of this amount should be considered a post-partum hemorrhage.

With the experience gained in this study, we are confident that we can materially decrease the incidence of post-partum hemorrhage expressed either quantitatively or as a percentage of body weight.

Acknowledgement is made to the Associate Committee on Medical Research of the National Research Council for technical assistance through a grant to Professor G. Hunter.

#### REFERENCES

- (1) Calkins, L. A., Litzenberg, J. C., and Plass, E. D.: *AM. J. OBST. & GYNEC.* 21: 175, 1931. (2) Calkins, L. A.: *J. A. M. A.* 101: 1128, 1933. (3) Smith, W. S.: *New York State J. Med.* 31: 141, 1931. (4) Peckham, C. H., and Kuder: *AM. J. OBST. & GYNEC.* 26: 361, 1933. (5) Brandt, M. L.: *Ibid.* 25: 662, 1933. (6) Upshaw, C. B.: *J. M. A. Georgia* 23: 55, 1934. (7) Dieckmann, W. J., and Dailey, E. F.: *AM. J. OBST. & GYNEC.* 30: 221, 1935. (8) Calkins, L. A.: *Ibid.* 29: 231, 1935. (9) Doerr, E.: *Zentralbl. f. Gynäk.* 59: 22, 1935. (10) Pastore, J. B.: *AM. J. OBST. & GYNEC.* 31: 78, 1936. (11) *Idem.*: *AM. J. Surg.* 35: 417, 1937. (12) Abramson, M., and Berman, I.: *AM. J. OBST. & GYNEC.* 35: 626, 1938. (13) Dorset, E. L.: *J. Missouri M. A.* 36: 99, 1939. (14) Starr, S. H.: *Kentucky M. J.* 37: 120, 1939. (15) Beecham, C. T.: *AM. J. OBST. & GYNEC.* 37: 258, 1939. (16) Pastore, J. B., and Stander, H. J.: *Texas State J. Med.* 35: 390, 1939. (17) Smith, R. G.: *J. A. M. A.* 111: 2201, 1938. (18) Davis, M. E.: *AM. J. Surg.* 48: 154, 1940. (19) Cosgrove, S. A.: *South M. J.* 29: 1219, 1936. (20) Conn, L. C., and Vant, J. R.: *Canad. M. A. J.* 33: 484, 1935. (21) *Idem.*: *Ibid.* 35: 281, 1936. (22) Pastore, J. B.: *AM. J. OBST. & GYNEC.* 32: 859, 1936. (23) Plass, E. D., and Bogert, L. J.: *Johns Hopkins Hosp. Bull.* 35: 361, 1924. (24) Stander, H. J., et al.: *Surg., Gynec. & Obst.* 31: 276, 1920; *Johns Hopkins Hosp. Bull.* 35: 1, 1924. (25) Weech, A. A., and Reeves, F. B., and Goettsch, E.: *J. Biol. Chem.* 113: 93, 1933.

#### DISCUSSION

DR. FRED L. ADAIR, CHICAGO, ILL.—Hemorrhage is of course extremely important from the standpoint of the deaths it causes, but it also has an effect upon the recovery of the patient which, I think, has not been sufficiently appreciated.

We must, of course, recognize what we might call physiologic blood loss. I do not think anyone would entertain the idea that a woman could be delivered and

DR. GEORGE KAMPERMAN, DETROIT, MICH.—The measurement of blood loss gives as a rule figures more accurate than mere estimations, but even actual measurement may not be positively accurate. Dr. Conn confesses in his paper that even in making measurements there is a certain amount of estimation. He admits this when he states that the amount of "after waters" usually balances the amount of blood which collects on the linen. We believe these studies have a great academic value, in that they give us certain fundamental information, and it emphasizes facts of which the medical profession is not entirely conscious.

There is a distinct individual variation as to reaction to loss of blood. Patients who lose larger amounts may show little change in their general condition. Patients with smaller blood loss may require transfusion while patients with larger amounts of blood loss may not show such need. Pastore has, however, pointed out that patients with large blood loss may make better post-partum recoveries, if blood is replaced by transfusion, even if at delivery a transfusion may not have seemed urgent.

It has long been our opinion that management of the placental expulsion is the greatest factor in blood loss. The study of Calkins, Litzenberg and Plass did not show that length of first and second stages of labor affected the amount of blood loss, but the report did indicate the importance of the length of the third stage. In Dr. Conn's paper he did not differentiate between the influence of the various stages. Perhaps if he would break down the statistics shown in Table IV it might give a conclusion similar to that of Calkins, Litzenberg, and Plass.

Our earlier teaching was not to interfere with the placenta until a half hour had passed. Now it is recognized, and emphasized by Dr. Conn, that placental separation occurs much sooner. We believe the importance of recognition of placental separation cannot be overemphasized. And we believe it is equally productive of excessive hemorrhage if the removal of the placenta is attempted before separation, as it is if the placenta is not expressed as soon as separation has occurred.

It is not simply a question of waiting, but rather watching and recognizing the signs of placental separation. While the hand on the uterus may be an important factor in preventing hemorrhage by recognizing the condition of the uterine fundus, it all depends on whose hand it is and whether the individual recognizes the purpose of the hand on the uterus. Often this important observation is left to the least trained nurse. Too often the hand indulges in unwarranted massage which may be productive of unnecessary bleeding. In general the uterus should be massaged only when relaxed and bleeding, and not pushed down into the pelvis. Rather it should be displaced upward out of the pelvis.

Some of the procedures of the newer obstetrics may be factors in causing additional bleeding. According to the statistics presented by Dr. Conn, the ordinary outlet forcep, practiced now so frequently with little obstetric indication, is productive of additional bleeding. It all depends on who does it and with what skill and under what conditions the procedure is undertaken. It would seem other factors than low forceps must be the cause of this additional blood loss.

The same comment can be made about the blood loss attributed to episiotomy. We believe the hemorrhage from such an incision should be as controllable as hemorrhage from any surgical incision, and doubtless more so than hemorrhage from a laceration. Furthermore, Dr. Conn reports in 2,000 cases only 5 complete lacerations of the perineum, but each with definitely increased blood loss. Is it not possible that episiotomy in this series of Dr. Conn's may have reduced the number of the more extensive lacerations?

It seems correct to infer from such a study as Dr. Conn has made that the cause of excessive bleeding lies often in certain uncontrollable and unavoidable factors. In such groups the obstetrician's duty is to counteract the results of blood loss and to anticipate this in many instances. We believe blood transfusions should be made more available, easier and should not be so difficult as to be impracticable. The establishment of a blood bank is the best insurance against bad results from hemorrhage. It is significant to note how the number of transfusions increase when a blood bank is available. With a blood bank available, it is just as easy to give a transfusion of blood as it is to give intravenous saline or glucose. We also

We believe that this method diminishes blood loss, steps up the second stage and promotes shorter and better convalescence of the patient. Furthermore, it has reduced the incidence of manual removal of the placenta and of the other intra-uterine manipulations for the purpose of controlling post-partum hemorrhage. For example, in 1936 and 1937 we had 33 uterine packings, and in 1939 and 1940 we had only 2 uterine packings, both because of trauma. The atonic type of hemorrhage has been practically eliminated.

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—Of all of the factors contributing to blood loss in delivery listed by Dr. Conn, I would especially emphasize mismanagement of the third stage. I personally approve the principle involved in the method of keeping the uterus elevated out of the pelvis and expelling the detached placenta from the lower uterine segment by manipulation of that portion of the uterus rather than of the fundus. One cannot, however, be too slavishly addicted to any method. The resourceful obstetrician will modify methods to meet needs. For instance, if there is a tendency for the isthmus of the uterus to contract and incarcerate a separated placenta, only pressure on the fundus will overcome the obstruction and expel the placenta from the uterine cavity.

In our clinic we have run the gamut of injecting pituitrin, the ergot alkaloids, and ergotocin, as each of these several products have become successively available. From time to time we have used both the intramuscular and the intravenous routes. The time of such injections has varied from that of the expulsion of the baby's head through the introitus to the completion of the third stage of labor.

My practice, employed for a period of about a year, is to inject intravenously 1/320 gr. of ergotrate as soon as the baby's head is delivered over the perineum. During the same period of time other chiefs of service in our clinic have followed somewhat different practices. The following are the comparative results obtained by four methods:

ERGOTRATE GR. 1/320	INTRAVENOUS		INTRAMUSCULAR	
	AFTER EXPULSION OF HEAD	AFTER EXPULSION OF PLACENTA	AFTER BIRTH OF BABY	AFTER EXPULSION OF PLACENTA
No. of cases	854	542	81	487
Average duration third stage	7.9	8.7	10.7	8.9
Average blood loss	137 c.c.	170 c.c.	205 c.c.	173 c.c.
Repeated oxytocic necessary	29 cases or 3.3%	14 cases or 2.5%	11 cases or 13.5%	37 cases or 7.5%
Incarceration	17 cases or 1.99%	*5 cases or 0.9%	0	0

\*This of course had no relation to the oxytocic, but when related to the whole group of 1,029 cases (sum of second and third columns), which received no oxytocic before delivery of placenta, an incidence of 0.4 per cent, it does give a basis on which to assess the incidence when oxytocic is used as in Column 1.

I further resort more promptly than formerly to manual extraction of the placenta in the event of failure of spontaneous expulsion in response to oxytocics administered as indicated and mechanical manipulation employed. For I have been impressed with the great blood loss represented by apparently insignificant oozing over a period of several hours. Such oozing is never measured nor is attempt very frequently made even to estimate it. The effect, however, on the patient's constitutional condition and subsequent degree of anemia indicates that such blood loss may be astonishingly large and deleterious. I believe that prompt, careful invasion of the uterus is less dangerous than such hemorrhage.

The emphasis placed on certain other factors will vary with the competence of management. Operative delivery per se does perhaps add to the blood loss but hardly to a very large extent if such operative procedures are based on proper indications and conditions and competently carried out. On the other hand, such interference if not judiciously and expertly employed may become a factor in most serious blood loss. Particularly is this so if such ineptness directly causes the lacerations which are such important causes of hemorrhage.

## ECTOPIC PREGNANCY\*

### SELECTIVE DATA FROM SIXTY-FIVE CASES

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ECTOPIC pregnancy appears in our practice and in the general statistics about once in every 200 operative gynecologic cases. It occurs once to about every 300 intrauterine pregnancies.

The material for this study is based upon 65 cases in which the pathologic diagnosis was ectopic pregnancy. Fifty-four of these are from the gynecologic-teaching service of the University of Oregon Medical School, eleven cases from the author's practice. All were seen between January, 1931, and January, 1941. Patients in whom the diagnosis of ectopic pregnancy was incorrectly made are not included.

*Age and Parity.*—The largest number were noted in the five-year period between 25 and 30 years (17 cases). There were 16 patients between 20 and 25 years; 10 patients between 30 and 35 years; 16 patients between 35 and 40 years. There was one patient under 20 years, one over 40 years.

The incidence in relation to parity reveals that the largest group (26 cases) occurred in patients who had been pregnant once before. The next largest (17 cases) was in patients with no previous pregnancies. In patients twice formerly pregnant there were 13; thrice formerly pregnant, 2; four times, 6. Nothing in these statistics departs notably from common knowledge. The fact that ectopic pregnancy occurred more frequently in women with one previous pregnancy than in previously childless women might argue in a general way against the stated frequency of ectopic pregnancy in women long sterile; nor are statistics relative to age and nulliparity significant. Only one patient in the nulliparous group reported previous treatment for sterility.

*Previous Laparotomy, Abortion, Pelvic Infection.*—Previous pelvic laparotomies appear to have been frequent in our series; 14 were reported (21 per cent). These figures are rather lower than in most series (Seheffey,<sup>1</sup> Langman and Goldblatt<sup>2</sup>), yet they support the conclusion that previous invasion of the lower abdomen for whatever purpose appears to contribute to the incidence of ectopic pregnancy. In 22 instances (34 per cent), previous abortions were reported, four of which were self-induced. Again this figure supports the evidence that previous abortion contributes to the incidence of ectopic pregnancy. Curettage, for whatever reason, had been done in 10 cases (15 per cent). The question of previous infection, per se, is so bound up in the matter of previous operations and abortions that it could not be separately elucidated. The frequent finding of an inflammatory reaction in the affected tube as well as in the opposite tube removed at the same operation is pertinent. It remains clear that while these factors have been noted somewhat less

\*Read, by invitation, at the Sixty-Sixth Annual Meeting of The American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

would like to emphasize that in the treatment of shock, resulting from hemorrhage, the use of blood plasma in untyped patients is very efficacious and seemingly more so than glucose or saline solution.

A most interesting part of Dr. Conn's paper concerns the study of serum proteins and specific gravity of blood serums. It almost reminds one of the old Calvinistic doctrine of predestination. The amount of blood lost at delivery seems to run parallel to the specific gravity of the blood serum. It seems plausible that one might be able to predict in advance which patients are going to lose blood excessively. We are also impressed by our own experience that patients who are anemic are also more likely to lose blood. The practical inference would be that if prenatal studies of blood could be made, those showing the factors which would prophesy excessive blood loss should be typed in advance and blood transfusions made available.

At Harper Hospital where blood loss is not accurately measured in all cases, and where the label of post-partum hemorrhage is attached because of the clinical condition of the patient, we find 31 such cases among our last 3,000 deliveries. We are well aware that other patients should be included as having had post-partum hemorrhage since doubtless many patients lost 600 c.c. of blood who showed little resulting reaction. Of these 31 patients 21 were primiparas, and 10 multiparas. Eighty per cent were over 25 years of age, 55 per cent over 30 years of age, and 6 per cent over 35 years of age. This means that by far the greater number were below 35 years of age. Among these cases the average primiparous labor was fourteen hours, and that of multiparas seven hours. Sixty-seven per cent had had some type of delivery interference, significantly a percentage far greater than the average percentage of interference in all cases. Of these 31 babies, 58 per cent were 8 pounds or over in weight. In 5 cases the uterine cavity was packed with gauze, and the morbidity among these was the same percentage (20 per cent) as among those not packed. We believe packing the uterine cavity may be resorted to in certain cases without fear of additional morbidity. Eight of these 31 patients had blood transfusions (15 transfusions). Among these cases there were 6 post-partum infections, or 20 per cent morbidity.

While we commend the measuring of blood loss during labor and recognize its importance from an academic standpoint, we do not believe that the delivery of patients without the measuring of blood loss is necessarily poor obstetrics. The recognition of the clinical picture is of greatest importance.

DR. CONN (closing).—Regarding the specific gravity of the serum, we do not know much.

From this small number of cases we do feel that if we get a very low value for serum proteins we would be very careful about giving sedatives. We would not do any episiotomies, would treat that patient very conservatively, and would watch the third stage of labor very carefully. Dr. Douglas, with whom I have been talking, has suggested that by giving plasma to these patients the condition might be changed considerably. This is only a preliminary report, and we are going to study this problem throughout pregnancy to see whether we can arrive at any conclusions.

*Concomitant Operations.*—In general, we regard as undesirable other operations, particularly elective, performed at the time of operation for ectopic pregnancy. In the presence of hemorrhage or suspected infection, the minimum surgical procedure to control the immediate emergency is called for. Analysis reveals, however, that we have departed considerably from this dictum, and our statistics, therefore, are of unusual interest. Concomitant operations are reported 28 times, including removal of one or both ovaries, both tubes, and all or part of the corpus of the uterus. This material should certainly offer statistics to emphasize the dangers of such practices. However, surprisingly, we find that the average number of hospital days for this group is no higher than for the entire series (nineteen days). The two deaths in our series did not occur in this group and our total death rate (3 per cent) is not out of line.

*Recurrent Ectopic Pregnancy.*—Incidentally, no patient in our series has returned with a second ectopic pregnancy. This is most unusual and may be due to the fact that so many of the patients were sterilized (18 cases—28 per cent), and had other pelvic pathology attended to. R. B. Smith<sup>5</sup> reported 3.6 per cent second ectopies in 1,608 patients operated upon by members of the American Gynecological Society; others<sup>6-8</sup> report incidences up to 22 per cent. The necessity for later pelvic surgery is frequent as reported in published statistics. These figures then, whatever one's personal convictions may be, must be submitted in defense of conservative surgery indicated on other growths, except in patients with free bleeding or infection. Incidentally, this thesis has its staunch advocates.

*The location of the pregnancy in the tube* was as follows: 31 (47 per cent) were in the infundibulum; 9 (14 per cent) were in the ampulla; 14 (21 per cent) were in the isthmus. There were one true interstitial pregnancy and one cornual pregnancy. The mass in five instances was apparently extratubal. These were classified as abdominal or broad ligament pregnancies but not so proven. No ovarian pregnancies were noted. The location was not stated in eleven cases. At operation 41 (63 per cent) were demonstrably ruptured and 23 (37 per cent) not ruptured.

*Hospitalization.*—The average number of hospital days was 16.3 including preoperative and postoperative days. Fifty-two patients were hospitalized less than three weeks (80 per cent); 11 from 21 to 30 days, and 2 patients 31 and 35 days, respectively. These figures coincide roughly with those of Scheffey,<sup>1</sup> Langman and Goldblatt,<sup>2</sup> and others.

*Mortality.*—There were two deaths in the series, and no deaths in the last eight years. Death occurred in one patient upon whom I\* operated, due to peritonitis. An error was made in surgical judgment in the attempt to remove a grossly adherent sac and placenta. The ovular remains should have been left, and the abdomen closed. The second death occurred in a woman who entered the hospital in shock, never rallied and died on the table in spite of immediate transfusion. The mortality rate was 3 per cent.

*Diagnosis.*—Our diagnosis was correct in 52 instances (80 per cent), and incorrect in thirteen instances (20 per cent). This figure does not include conditions diagnosed as ectopic pregnancy and found not to be. Incorrect diagnoses under which ectopic pregnancy was found at operation included five mistaken diagnoses of ovarian cyst, three of pelvic

\*Senior author.

frequently in our series than in most (Scheffey,<sup>1</sup> Langman and Goldblatt<sup>2</sup> and others), their frequency definitely points to them as important in etiology.

*Symptoms, Pain, Bleeding, Nausea, Fainting.*—The patient's first complaint was of pain in 41 cases, bleeding in 19 cases, simultaneous pain and bleeding in five cases. Nausea and vomiting were noted in 38 cases, apparently, however, quite definitely due to the acute illness as distinguished from morning sickness. Interestingly, out of these 38 patients, 13 had fainted, and in each of these 13 cases, rupture and hemorrhage were found to have occurred at or prior to the time of fainting.

*Tenderness, Pelvic Mass.*—Fourteen patients (21 per cent) complained early of generalized abdominal tenderness; 44 (69 per cent) complained of more or less localized lower quadrant tenderness; 6 (9 per cent) showed definite lower abdominal rigidity; a lower abdominal mass was outlined on abdominal examination in 24 instances (44 per cent); in 10 cases (15 per cent) the finding of a mass was questionable, and in 22 cases (32 per cent) no masses were felt. On bimanual examination a palpable mass was felt in either adnexal region or the cul-de-sac in 38 cases (58 per cent). In 10 instances excessive tenderness prevented satisfactory examination. The estimated size of these masses varied from 5 to about 15 cm. in diameter. Again, these findings do not depart notably from those recorded by others.

*Hematology.*—Details are available but will not be recorded here. However, certain observations appear justified: Less than 3 million red cells were counted in 14 cases (21 per cent); between 3 and 4 million in 18 cases (27 per cent); and over 4 million in 27 cases (41 per cent). The hemoglobin averaged over 60 per cent in 54 cases (88 per cent). The red count and hemoglobin estimation immediately following or during drastic hemorrhage generally failed to register the true blood depletion. Experience indicates that forty-eight hours must pass before reliable counts are to be expected. A twelve-hour wait appeared to increase the accuracy considerably. Consistently, however, falling red blood count and hemoglobin on repeated analysis reflected serious and progressive intraabdominal bleeding. White counts were increased as they may be expected to be in the presence of hemorrhage. Lilian Farrar called our attention to this phenomenon as long ago as 1925. The sedimentation rate was often accelerated in the presence of hemorrhage and in the absence of infection; and the readings were often as confusing as helpful. We were forced to conclude that the assistance in differential diagnosis usually offered by all of the blood work was too often obscured by the effects of anemia.

*Transfusion* was done 21 times; 4 times preoperatively, the remainder during or after the operation. Our experience indicates that the decision in regard to the best time to transfuse is absolutely dependent upon the patient's condition. However, except as a definite emergency, it has seemed best to conserve the donor's blood until the bleeding vessels are controlled. Autohemoclysis, wrongly called autotransfusion, was done in five instances, twice on the same patient whose case will be reported (Case 57). Three times it was thought to save a patient's life. We had no unfortunate experience with it. Shaw<sup>3</sup> reports its use 122 times, and Wallingford,<sup>4</sup> 28 times without accident. I believe it is to be recommended in emergencies when more suitable blood is not available. Otherwise, we have had satisfactory results from leaving all blood, including clots.



ectopic decidua. Furthermore, in this connection, the possible danger of the use of massive doses of progesterin in the treatment of sterility is to be considered as perhaps predisposing to premature implantation.

*Decidual Reaction in the Uterus.*—The true endometrium influenced by ectopic placentation theoretically obeys the usual hormonal influences in a perfectly typical manner. It is now well established that the changes which occur after or during the demise of the ovum are in all respects similar, not only to those of menstruation, but, on a relative scale, to those of abortion or miscarriage, and of the third state and puerperium. This matter was discussed before the American Gynecological Society in 1939 after the presentation of a paper by Dr. Harold O. Jones. At this time Drs. TeLinde, Corner, and Schwartz drew attention to the similarity in the behavior of estrin and progesterin concentrations.

From the above, certain practical, or we might say, clinical corollaries evolve: (1) So long as the progress of the ectopic gestation is undisturbed, the development of the uterine decidua will follow its usual pattern (minus fetal elements). In two of our cases, one carried to four and one-half and one to five and one-half months, no uterine bleeding occurred, precisely as in a normal pregnancy. The more meticulous observers (Veelman, Solomons) have indicated discernible differences in this special decidua, involving chiefly the nature of the gland structure and stratum compactum. There seems however to be general agreement that such differences are minor except for the fetal components. (2) Abrupt death of the ovum, or its operative removal, generally results in early and complete evacuation of the intrauterine decidua, frequently as a decidual cast. Damage to the ovum with gradual disruption of chorionic integrity results in concomitant damage to the intrauterine decidua, generally exhibited as irregular bleeding with partial or delayed disposal of decidua. Jones and Brewer have demonstrated that this process is contingent upon physiologic vascular constriction of the circular arterioles, in all respects similar to the bleeding and disposal mechanism of menstruation.

For use in diagnosis these observations may be conveniently arranged as follows: (1) The passage of an endometrial decidual cast without demonstrable chorionic villi is not only virtually diagnostic of ectopic pregnancy, but generally reflects sudden death of the ovum, spontaneous or operative. Interestingly, a decidual cast was found or reported in seven of our series. Two were discharged a few days after operation, 3 after acute rupture, yet 2 were reported by the patient with the pregnancy unruptured at subsequent operation. (2) Only presumptive evidence of ectopic pregnancy is offered by the finding of decidua in the lochia of suspect irregular bleeding, or by its absence. This is true also of curettings. Naturally, such an investigation is generally in the interest of a differentiation between abortion in progress and ectopic pregnancy. The failure to find chorionic villi in such lochia or curettings cannot be regarded as excluding their presence since the tissue may not have been obtained from the basalis; in other words, placental tissue may be present in the uterus but not in the material for examination; or it may not be found by the microscopist; furthermore, a decision as to the absolute histologic characteristics of the recovered tissue may be impossible.

The decidual reaction in the uterus itself during ectopic pregnancy is chiefly of interest in relation to claims which have been made for the

inflammatory involvements and miscellaneous conditions (threatened abortion, ruptured gall bladder, acute pancreatitis, pregnancy in incarcerated retroverted uterus, fibroid uterus with pregnancy). We correctly diagnosed unruptured pregnancy in 13 instances. I believe that our diagnosis has been definitely improved by the routine use of the Friedman test and the frequent use of the cul-de-sac puncture. These will be discussed later.

*Ectopic Endometrial Tissue.*—Misplaced or aberrant endometrial tissue is occasionally found in connection with ectopic pregnancy. A typical decidual reaction in the capsule of an ectopic pregnancy is frequent, and has generally been ascribed to heteroplasia<sup>9</sup> rather than to the previous presence of true endometrial stroma cells in such an area. It was clearly described in 10 of our cases and doubtless present in more. Frankel and Schenk<sup>10</sup> have been able to demonstrate a decidual reaction in the immediate vicinity of almost every ectopic pregnancy which they have investigated. Langman and Goldblatt<sup>2</sup> in a careful study of their pathologic material were unable to confirm these observations. In one of our cases, Watkins noted and photographed typical decidual reaction in a cul-de-sac endometrioma accompanying an intrauterine pregnancy. In our Case 56, a decidual reaction was noted in an adenomyoma of the Fallopian tube opposite an interstitial pregnancy, and glands were noted in the subserosal myometrium underlying the ovum itself. The evidence here is most convincing of an adenomyomatous area as the cause of arrest of the ovum in this tube (Figs. 1, 2, and 3).

This theory that ectopic endometrium under normal corpus luteum influence may attract and hold the ovum is engaging, and has considerable backing, although the occurrence is doubtless rare. The theory that an abnormally active (nonpregnant) progestational influence may create an unusually receptive nidus for ectopic implantation is also of interest, but also still theoretical. It is indirectly supported by the observations of TeLinde and Henriksen<sup>11</sup> and others, who found almost perfectly developed decidua independent of pregnancy, under hyperprogestational influence, generally accompanying corpus luteum cyst, and often associated with delayed menstruation. May I, at this time, also signalize the basic work in this field done by Litzenberg, at a time when our concepts of the histology of ectopic placentation were very fragmentary.

*Corpus Luteum Influence, Increased Progesterone Concentration.*—The frequent association of corpus luteum cyst with increased progesterone concentration may eventually prove to be of interest in relation to the causes of premature implantation. Ectopic endometrium or even simple decidual stroma might theoretically be so affected by this extra progesterone as to create an excellent site for premature implantation. However, in our series, among twelve patients with ovarian cyst only four were true corpus luteum cysts, and four single or multiple cystic corpora lutea. Frankel<sup>10</sup> and Ehrhardt<sup>12</sup> both found ovarian cyst in one out of every three ectopic pregnancies, but do not specify corpus luteum cyst. It may also be of interest that in all of the patients with corpus luteum cyst or cystic corpus luteum in our series, the pregnancy occurred in the distal third of the tube, indicating even earlier implantation than usual. These findings are certainly not more than vaguely suggestive, but similar observations should routinely be made in larger series. It must not be forgotten that certain authors (notably Frankel), hold out staunchly for the almost constant etiologic association of ectopic pregnancy with

record of 88 examinations with this diagnosis in question. He says the decision was routinely correct and no harm resulted. Recently, with the assistance of Dr. Paul Spangler, I inspected the pelvis of a young woman thought to have a right tubal pregnancy. I saw clearly a large, congested, prolapsed and adherent right ovary with a corpus luteum of pregnancy. The abdomen was not opened and the patient delivered normally seven months later. The procedure is considerably more ambitious than cul-de-sac puncture. It is painful and disturbing to the patient, requires special knowledge and has some dangers. It is difficult to say how important a place it may assume in our diagnostic equipment.



Fig. 1.—(Case 56.) Interstitial pregnancy in right cornu. The tubal structure is completely obliterated and decidual reaction is widespread. Gland structure is demonstrable throughout. The opposite (left) tube contains two lumpy enlargements both hemorrhagic on gross section; both unmistakable adenomyomas of the Fallopian tubes.

#### CASE REPORTS

CASE 56.—A white female, aged 41 years, gave a history of four spontaneous early abortions, one delivery at term, no pregnancies for seven years. The clinical picture at admission was noncommittal between incomplete abortion and ectopic pregnancy. The Friedman test was positive. Curettage resulted in a dry scrape. The abdomen was opened. The body of the uterus, right tube and ovary and left tube were removed. The right horn of the uterus was the site of a walnut-sized protrusion, incision of which revealed an intact interstitial pregnancy (Fig. 1) surrounded on all sides by gland-containing myometrium. The tubal structure was completely obliterated and decidual reaction was widespread. The opposite tube contained two lumpy enlargements, both hemorrhagic on gross section. These proved to be unmistakable adenomyomas of the Fallopian tube.

Fig. 1 is a photograph of the specimen. The interstitial pregnancy is visible at the right cornu. Fig. 2 is a low power magnification of a section cut obliquely through the right cornu. *Se* indicates uterine serosa; *En* indicates endometrium; *IP* indicates the interstitial pregnancy. The square in the upper left corner is enlarged in Fig. 3, showing unmistakable glandular structure in the subserosal myometrium. Decidua was present in the immediate vicinity. Fig. 4 enlarges the same area.

diagnostic value of curettage. We have had for examination curettings from 6 patients with ectopic pregnancy, the vault of the uterus removed from 8 patients, and 3 decidual casts.\* This material has been carefully reviewed with an eye to its potential value in diagnosis. Of these 17 endometriums, only 6 showed a typical decidual reaction; 4 showed hyperplastic endometrium in some areas suggestive of progestational influence; 5 showed normal interval endometrium; one curettage resulted in a dry scrape. These findings cannot be considered even potentially helpful from a diagnostic point of view. In other words, had curettage been done in all of these cases, the diagnosis would have been assisted in only 6 out of 17, and definitely confused in the remainder. Naturally, the finding of chorionic villi in the uterus is diagnostic of intrauterine pregnancy. Yet the finding of decidua in the uterus without villi does not exclude the presence of placental tissue which may have been missed by the curette or by the microscopist. Since, therefore, curettage as a diagnostic measure has some objectionable features under such circumstances, its use should doubtless be restricted.

*Aschheim-Zondek or Friedman Tests.*—The unsupported statement is too often made that these tests have little or no diagnostic value in ectopic pregnancy. More recent careful observations indicate that, as in intrauterine pregnancy, it reflects accurately the presence of live trophoblast. I am convinced that its more frequent use accounts for the improvement in diagnosis noted in our series in the last four years. Henry Shaw<sup>3</sup> reports the use of the test in 61 cases and finds it reliable. It was made 19 times in our series. Of these 19 tests, 16 were positive. The three negative reactions occurred in patients who proved to have ruptured, nonviable ectopic pregnancy. The test has returned correctly positive in so many cases where there have been bleeding, cramps, signs of infection and other confusing factors, that we are encouraged to rely more upon it as time goes on. Naturally it is useless in differentiating intrauterine pregnancy, and may be confusing in the presence of ovarian cyst.

Briefly, it appears that the Friedman test has helped us as follows: Obviously a positive reaction is significant; but it does not differentiate a disturbed intrauterine pregnancy. A negative reaction does not exclude ectopic pregnancy nor all of its potential danger. I believe, however, that a negative reaction in a case which is not emergent is very helpful indeed. It is understood that the patient's condition, regardless of the negative Friedman reaction, will actually determine the management. A negative reaction, however, in the presence of a questionable diagnosis, may occasionally justify temporizing, and has more than once saved us from entering the abdomen under a mistaken diagnosis.

*Colpopuncture.*—Puncture of the cul-de-sac for diagnosis has been of signal assistance in our series. Done twelve times without apparent harmful effect, it has yielded conclusive positive results eleven times. A colpotomy was similarly helpful in one instance. In view of general experience, a cul-de-sac puncture by needle seems the more desirable procedure. Preparations for laparotomy should, of course, be complete.

*The peritoneoscope* was used for diagnosis by Shaw<sup>3</sup> in 11 cases without accident. In 10 cases the blood noted in the pelvis issued from a ruptured ectopic pregnancy. In the eleventh case, hemorrhage from a ruptured follicle was mistaken for that from an ectopic pregnancy. John Ruddock<sup>13</sup> who devised the instrument writes me that he has

\*One case was not suitable for microscopic study.

third) of the Fallopian tube. Immediate closure was effected. The patient was transfused and recovered without notable event. The sac wall was composed of smooth muscle and connective tissue. Decidual reaction was demonstrable and the lining epithelium was cuboidal. A section of normal Fallopian tube was identified on the anterior aspect of the tumor, 5 cm. in length.



Fig. 4.—(Case 56.) High power of glandular structure underlying the serosa.

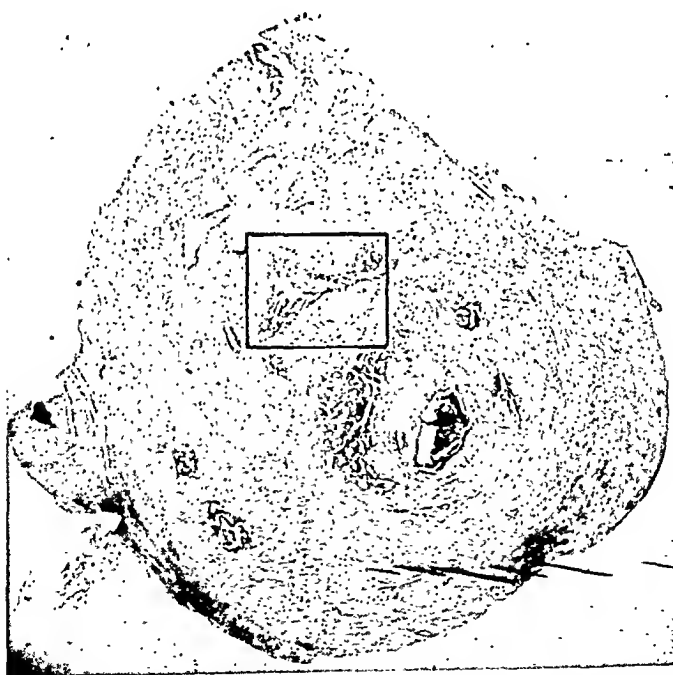


Fig. 5.—(Case 56.) A section cut through an adenomyoma in the opposite (left) tube an inch from the uterine cornu. Tubal lumen is to the right and below the square. The square encloses an adenomyomatous area.

Twenty-four days later, without warning, the patient had another tragic intra-abdominal hemorrhage. Her husband made the diagnosis, reporting by telephone a definite bluish discoloration of the navel which he said made him suspect blood in

Fig. 5 is a section cut through an adenomyoma in the opposite (left tube) an inch from the uterine wall. Fig. 6 enlarges the glandular area enclosed by the square, as does also Fig. 7, showing typical adenomyomatous structure with decidual reaction and some inflammatory change.

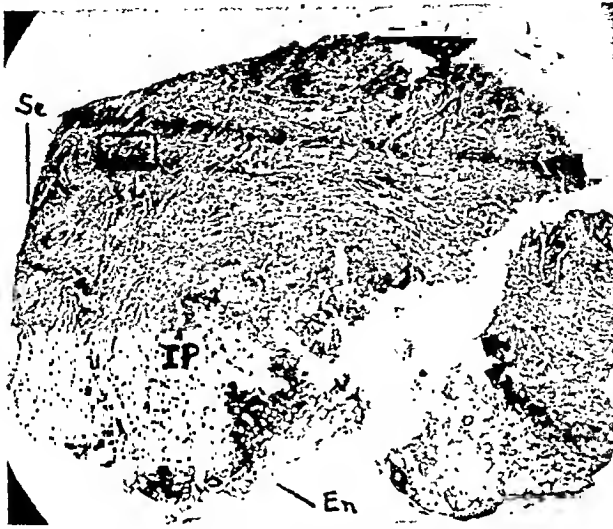


Fig. 2.—(Case 56.) Low power of microphotograph of section cut obliquely through interstitial pregnancy. *Se* indicates uterine serosa; *En* indicates endometrium; *IP* indicates interstitial pregnancy. An area is selected as indicated by the square underlying the serosa in the upper left corner.

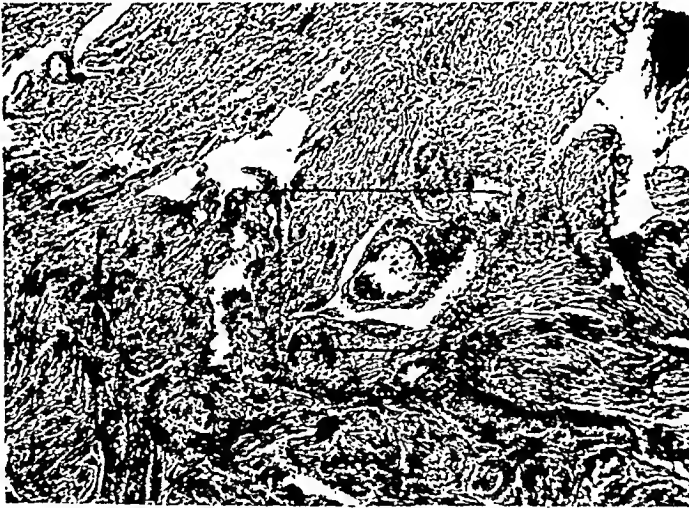


Fig. 3.—(Case 56.) Enlargement of enclosed area from Fig. 2. Subserosal endometrial gland.

CASE 57.—A healthy young woman developed what was taken to be a five and one-half months' pregnancy, without pain or irregular bleeding. She was not under my care until she suddenly developed severe pain in the epigastrium which spread rapidly as she went into shock. At laparotomy 1,200 c.c. of blood was obtained for autohemolysis, over one and one-half quarts being present.

In the pelvis there was a discrete spheroid mass, 15 cm. in diameter, bleeding from a split in its serosa similar to the splitting of the skin of ripe fruit. This tumor was adherent nowhere except at its pedicle (5.0 by 0.5 cm.) which took origin from the posterior aspect of the broad ligament above the mesovarium and below the Fallopian tube. It was clamped and transected with the adjacent portion (middle

CASE 58.—A 25-year-old white female, gravida ii, developed an apparently normal pregnancy to four and one-half months. She had no pain, tenderness or other unusual symptoms until four days before operation, when she suddenly developed sharp epigastric pain, later running through the entire lower abdomen. She was operated upon because of signs of intraabdominal hemorrhage. A discrete spheroid

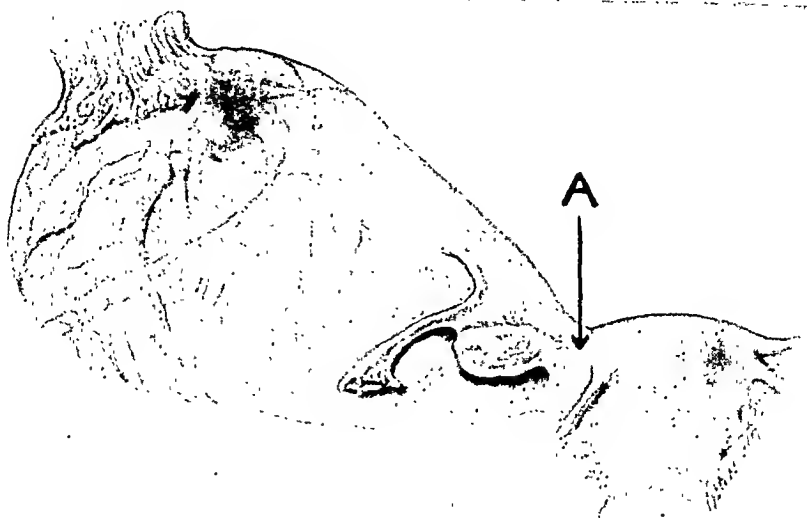


Fig. 8.—A drawing of the ectopic pregnancy from Case 58. The tumor has enlarged posteriorly, bringing the tube and ovary to the front. The distal tube merges with the cavity. No lumen or tubal structure is demonstrable in the pedicle at (A).

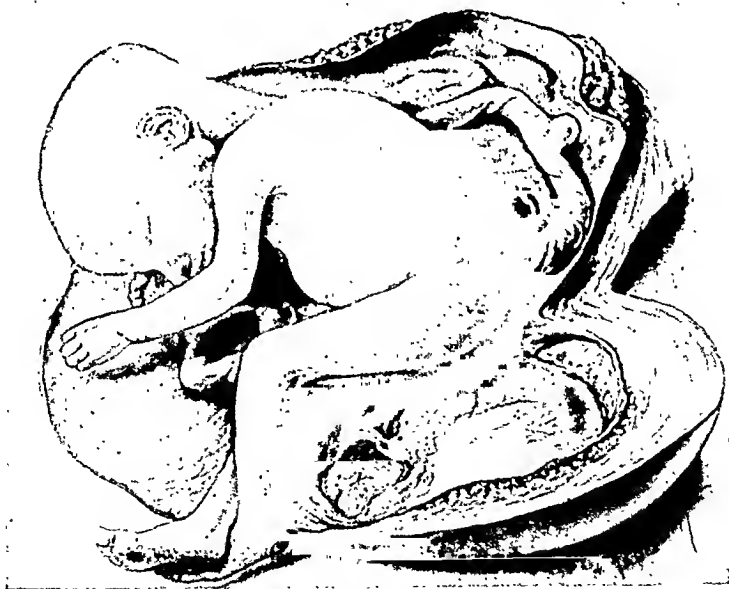


Fig. 9.—The opened tumor reveals a four and one-half months' pregnancy. The wall was thick, approximately normal myometrium, lined by glandular cuboidal epithelium with definite decidua.

tumor about 8 cm. in diameter was found pedunculated from the right uterine cornu (Fig. 8). The ovary was distal to the mass; the distal end of the tube clearly entered the mass. The pedicle from the uterus measured 1.5 by 4 cm. and on careful serial section revealed typical myometrium with absolutely no evidence of lumen of other connection with the uterine cavity. Fig. 9 shows the tumor opened.



the abdomen (the first Cullen's sign, to our knowledge, ever noted by a layman and correctly interpreted). The abdomen was again opened; transfusion and auto-hemoclysis were performed at once. Blood was found issuing from a large vessel on the dorsum of the right ovary thought to be a recently ruptured follicle. The

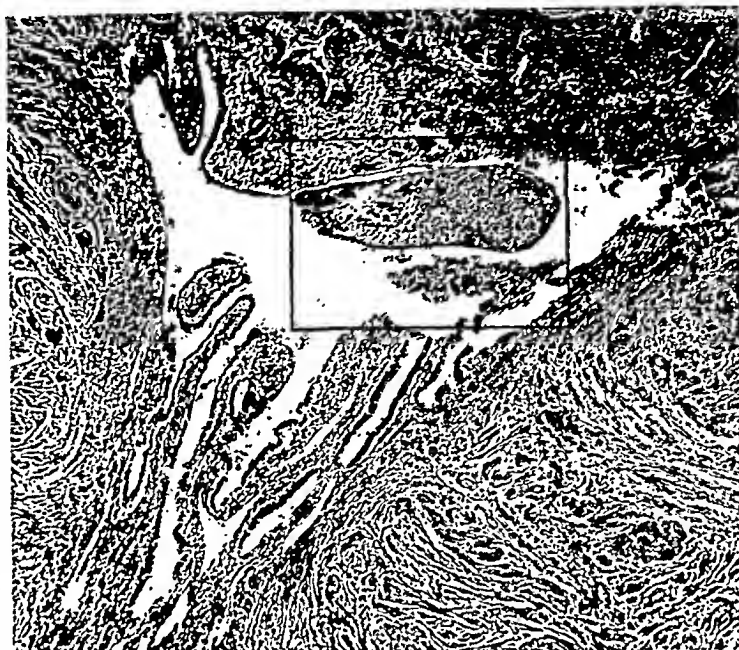


Fig. 6.—(Case 56.) Enlargement of area enclosed by square in Fig. 5. Endometrial glandular structure with decidual reaction and inflammatory change.



Fig. 7.—(Case 56.) High power showing decidual reaction and glandular structure. This is *not* salpingitis isthmica nodosa.

ovary and remainder of the tube were removed, revealing the proximal and distal ends of the tube intact, and connected by a scarred area in the isthmie portion (portion removed on the tumor at former operation). Recovery occurred without notable event and the patient at the present time (a year later), following a successful tubal insufflation, is normally pregnant at six months.



matory disease, and these abortions had caused a mild pelvic inflammation which in turn was the cause of the ectopic. In my own series of over 300 ectopics, I know of only one case where a previous operation had been the etiologic factor and here a Gilliam suspension had been done and the operator had shortened the round ligament so much that it had caused a definite kink in the tube.

Every one realizes that the extent of the operation performed for an ectopic depends on the location of the pregnancy and the condition of the patient. If the other tube is left in there is of course a definite danger of a second ectopic, as has happened in quite a number of my own cases. Still so many of these women do have normal intrauterine children later, if one tube is left, that it seems unwise to sterilize these patients as a routine measure.

We have had very little help in the diagnosis of ectopics from the Friedman and Aschheim-Zondek tests. At the present time we are having much more satisfactory results with the Falls test. A recent case of unruptured ectopic was diagnosed just twelve days after the patient had missed her menstrual period. The Falls test is much more rapid, taking only an hour for the reaction instead of two days with the others, as well as being much more easily done and less expensive. Most cases of ectopic pregnancy present a sharp, clear-cut picture, with a definite history and clinical findings which make the diagnosis in most cases fairly easy without any laboratory help.

Dr. Schauffler's findings of endometriosis in his ectopics is interesting. This misplaced endometrial tissue may play a much larger part in the etiology of these cases than we now suspect, especially in those cases where there is an adenomyomatous condition of the uterus.

I should like to mention here one fact which to my knowledge does not appear in any of the textbooks and which is of great importance in the diagnosis of ectopic pregnancies which go beyond the early stage. The cervix in abdominal pregnancy corresponds in size and consistency to the pregnancy above it, and not to the size of the uterus itself. This was first pointed out to me by Dr. Kelly and to him should go the credit for the observation. Four members of this Association who were then house officers had examined a patient with a supposed large ovarian cyst and in whom there was no history or suspicion of pregnancy. Dr. Kelly at once pointed out that the cervix was the size and softness of a full-term pregnancy, but the uterus only slightly enlarged. He made an immediate diagnosis from this of a living seven and one-half months' abdominal pregnancy and operated, removing not only the living fetus from its sac, but the entire placenta as well, as it was receiving its entire blood supply from the omentum. Since then this enlargement and softening of the cervix have been found to be present in all of the advanced abdominal pregnancies I have seen. This condition cannot be due in these cases to an increased blood supply as in normal pregnancy, but must be due to some endocrine action of which we as yet do not know.

One further suggestion I should like to make to prevent future trouble is that, even in simple-appearing, unruptured ectopics, tissue should be examined from various portions of the tube so as to pick up a possible chorionepithelioma, as this developed later in one case of my own and was not detected in the single block of tissue cut for diagnosis but found in the block cut later very close to the uterus.

Last, I would like to demonstrate to you an interesting and probably unique specimen (Fig. 1). This patient had missed her period a few days, and while walking on the street was taken with an acute agonizing pain and fell in a collapse. She was taken into a New York hospital, the diagnosis was made of an acute, ruptured tubal pregnancy, and she was operated upon immediately by the Resident. The right tube was removed and a cystic left ovary. Some six years later this patient moved to Baltimore and was referred to me after having experienced a twelve-day delay in her period and then a rather muddy discharge for about fifteen days. She complained of a slight pain in the right side where the previous ectopic pregnancy had been. On examination I could feel a slight enlargement in the cornu of the uterus, and thought that possibly at the previous operation a small stump of the tube had been left where a secondary ectopic had occurred. At operation the following morning I found this unusual condition. The right cornu of the uterus had been resected in New York, and shining through the cornu of the uterus with only a thin

## SUMMARY

1. Sixty-five cases with the pathologic diagnosis of ectopic pregnancy are reviewed. For this report some general considerations are omitted in favor of the more pertinent and timely aspect of the problem.

2. The impression that previous operations, abortions, and pelvic infection contribute to the incidence of ectopic pregnancy is supported by our findings.

3. Hematology and blood pressure observations support generally accepted conclusions. Our experience with transfusion parallels that of most other observers. Autohemoclysis, as an emergency measure, has been used with consistent benefit, where more suitable blood is not available.

4. In 28 cases surgery other than removal of the ectopic pregnancy was performed but not in the presence of infection or free bleeding. These patients did exactly as well as the rest of the group. It is thought that this surgical attention may account for the fact that no second ectopics are recorded (28 per cent sterilized). Other reported incidence is 3.6 to 22 per cent.

5. Our mortality rate is 3 per cent. Diagnosis was 80 per cent correct. The routine use of the Friedman test has improved our percentage of correct diagnoses.

6. Seventeen endometriums were available for pathologic examination. Had these tissues been obtained by curettage, diagnosis would have been assisted in only 6 out of the 17 and definitely confused in the remainder.

7. Microscopic examination of the tubes and other tissues indicates some further basis for the hypothesis of ectopic placentation in areas of ectopic endometrium or decidua.

8. Cul-de-sac puncture has been harmless and exceedingly valuable in diagnosis. The peritoneoscope has been used. Its status is discussed.

9. Three unusual cases are reported and illustrated.

Acknowledgement is made to Dr. Raymond E. Watkins for advice and assistance in the preparation of this material; to Dr. Herbert H. Foskett for the histologic studies; and also to Dr. William M. Wilson who operated upon the patient described in Case 58.

## REFERENCES

- (1) Scheffey, Lewis C., Morgan, Thomas R., and Stimson, Cheney M.: *AM. J. OBST. & GYNEC.* 24: 103, 1932. (2) Langman, Louis, and Goldblatt, Myron: *Surg., Gynec. & Obst.* 69: 65, 1939. (3) Shaw, H. N.: *Western J. Surg.* 48: 181, 1940. (4) Wallingford, Arthur J.: *New York State J. Med.* 37: 1922, 1937. (5) Smith, Richard B.: *Surg., Gynec. & Obst.* 18: 684, 1914. (6) Rubin, I. C.: *Ibid.* 24: 443, 1917. (7) Sserebroff, A. T.: *Arch. f. Gynäk.* 364: 148, Sub., 1932. (8) Mukuda, T.: *Jap. J. Obst. & Gynec.* 20: 427, 1937. (9) Marchetti, Andrew A.: *AM. J. OBST. & GYNEC.* 40: 69, 1940. (10) Frankel, J. M., and Schenk, S. B.: *Ibid.* 33: 393, 1937. (11) TeLinde, R. W., and Henriksen, Erle: *Ibid.* 39: 733, 1940. (12) Ehrhardt, K., and Kramann, H.: *Zentralbl. f. Gynäk.* 60: 2642, 1936. (13) Ruddock, John: Personal communication.

## DISCUSSION

DR. DEWITT B. CASLER, BALTIMORE, MD.—Dr. Schaufler comments on the fact that many of these patients have had previous abdominal operations and many a history of repeated abortions, and he believes that these contribute to the incidence of ectopic pregnancy. I cannot find myself in agreement with this view, but believe that these abdominal operations were probably for previous pelvic inflam-

purposes. Decidual reactions were reported in approximately 10 per cent, while the passage of a decidual cast was only established definitely in four instances. We concur with the essayist and others that curettage has a limited and selective value in diagnosis.

Biologic tests for pregnancy have a relative value and are necessarily reserved for differential diagnosis of the suspected case. Previous to 1932, the test was only used twice in our series; both times it was positive and ruptured tubal pregnancies were found. Since then it was employed in approximately 35 per cent of patients with proved ectopics, and in 45 per cent of patients finally evidencing other conditions, but in whom ectopics were suspected.

Of 43 patients correctly diagnosed preoperatively and proved at operation to have ectopics, the test was positive 11 out of 12 times. The negative test occurred in a so-called "old" ectopic. Of 19 patients incorrectly diagnosed primarily, but in whom operation revealed an ectopic, the test was positive 6 out of 10 times. (Two negatives were in suspected pelvic inflammatory cases, one in a supposed retroflexion of the uterus and one in a patient regarded as having had an abortion.)

Of 48 patients suspected of having ectopics but later proved otherwise, 21 tests were done of which 14 were negative and 7 were positive. (The 7 positives were all in patients having definite intrauterine pregnancies or complications thereof.) From these observations we think highly of the differential diagnostic value of such tests. The Friedman test has gradually supplanted the Aschheim-Zondek and Mazer-Hoffman procedures.

We are not in agreement with the essayist regarding cul-de-sac puncture, although in his hands it has been of distinct aid in making an accurate diagnosis 11 times out of 12. Successful aspiration assumes that a bulging, fluctuating mass is present in the cul-de-sac, and it seems to us that under these circumstances, colpotomy would be better from the aspect of drainage if pus were to be found, which possibility, in our opinion, is the principal indication for this differential procedure. If a fluctuating mass is not present, we think that aspiration might well damage the intestines. Incidentally we have not performed colpotomy in ten years; prior to that it was done ten times among 82 patients.

We believe that peritoneoscopy offers much in differential diagnosis of especially confusing cases. Dr. Kenneth Fry, of Surgical Service "A" at the Jefferson Hospital in Philadelphia, has developed an excellent technique for the procedure and has rendered us assistance recently in five instances. One confirmed a suspected diagnosis and was followed by immediate operation; four times the procedure revealed, respectively, intrauterine pregnancy, pelvic inflammatory disease, and cystic ovaries (twice). Dr. Fry also diagnosed positively three puzzling cases in which the patient was admitted to the Obstetric Service. We feel that peritoneoscopy is superior to either colpotomy or cul-de-sac puncture, and in our experience it has not been unusually distressing or particularly dangerous in the hands of one familiar with the technique.

Dr. Schauffler is to be congratulated on the correctness of diagnosis in 80 per cent of his patients. We were correct in 75 per cent. Among our incorrect preoperative diagnoses, pelvic inflammatory disease, and incomplete or threatened abortion were the principal conditions thought to be present.

As a matter of additional interest we have analyzed the case histories of 117 patients, admitted to the ward service during the same time, in whom a presumptive diagnosis of ectopic pregnancy was made. Twenty-eight of these patients (23.9 per cent) were operated upon as ectopics. About half of these patients had pelvic inflammatory conditions, the remainder revealing complications of intrauterine pregnancy, ovarian and retention cysts, etc. The sedimentation test has been of little value in differential diagnosis, for rapidity of sedimentation is indicative of tissue destruction; hence it is only "slow" in the unruptured case or where only slight leakage of blood has occurred.

Additional surgery when operating for ectopic is probably unwise, as Dr. Schauffler suggests in mentioning his figure of 50 per cent. Our own figure is 23.6 per cent, and while there were no fatalities in this group, the principle of essential surgery only had better be followed.

layer of intact peritoneum remaining was an interstitial pregnancy of an early date which was just about to rupture. The ovum of pregnancy had come from the right ovary and then by external migration had crossed over and gone down the left tube into the uterus, and then by internal migration had gone through the uterine cavity up into the right cornu of the uterus to become an interstitial pregnancy. Just why a fertilized ovum should take this circuitous route remains a moot question.



FIG. 1.

DR. LEWIS C. SCHEFFEY, PHILADELPHIA, PA.—My associate, Dr. D. M. Farrell and I have reviewed all the ectopic pregnancies that have been observed on the gynecologic ward service at Jefferson Medical College Hospital from Sept. 1, 1921, to Jan. 1, 1941. Our first analysis, published in 1932, included 82 patients; since then 62 additional patients have been observed on the ward service, making a total of 144.

All laparotomies should be taken into consideration when one considers the influence of previous surgery as an etiologic factor in the development of ectopic pregnancy. Appendectomy in girls and young women, whether or not associated with a suppurative process, is not infrequently followed by peritubal adhesions or occlusion of one or both fimbriae, as demonstrated by insufflation tests in sterility investigations. For the same reason any invasion of the abdominal cavity in the female may initiate conditions favoring ectopic nidation. Thirty-seven of our patients (25.6 per cent) had previous abdominal or pelvic surgery, or both.

I think, however, that abortion, either spontaneous or induced, prior to the ectopic gestation, has a greater incidence. Abortion had occurred in 56 of our patients (38.8 per cent), and in 11 of these it had been induced. Previous intrauterine procedures were recorded in 16 instances (11.1 per cent), and a previous ectopic in eight of our patients (5.5 per cent).

Preliminary curettage was performed in 38 cases (26.3 per cent). This includes patients in whom the diagnosis of ectopic pregnancy was not entertained at the time of operation. In clear-cut cases urgently in need of surgery, the procedure was properly omitted, but in some instances it was performed for investigative

## ON PREDICTING THE LENGTH OF LABOR\*

### I. FIRST STAGE

L. A. CALKINS, M.D., PH.D., KANSAS CITY, KAN.

*(From the University of Kansas Hospital)*

UNBIASED consideration of the physiologic process known as the first stage of labor would lead one to the conviction that two principal factors should be considered. The motive force is known to be, almost exclusively, uterine contraction. Resistance is provided by the cervix. Very little consideration has been given in obstetric literature to these two major factors in the various discussions of prolonged and difficult labor. Instead, the publications have dealt with age and stature of the mother, size of the pelvis, and size and presentation of the baby. There has been a great tendency to confuse difficult first stage and difficult second stage. We tried to show in our previous publication<sup>1</sup> that there was no correlation between the first stage and second stage and that, therefore, quite different factors must be presumed to govern the second stage from those having to do with the length and relative ease or difficulty of the first stage. We have previously demonstrated with respect to the first stage that such factors as maternal age and stature and pelvic size (within certain limits) do not have a demonstrable bearing on the length of, or difficulty involved in, that process. Infant size has no effect on the duration of the first stage in multiparas and little or no effect on primiparas. Occiput posterior has been said by all observers to result in a somewhat longer first stage than occiput anterior. At the time of our previous publication (1931), it was also our opinion that this was true. More recent information (to be presented in another communication) will prove this view fallacious. Abnormal presentation has been consistently looked upon as one cause of prolonged and difficult labor. Whatever the effect of abnormal presentation on the second stage, there is no particular reason to assume that it would necessarily prolong or otherwise make difficult the first stage of labor. We showed quite conclusively that this was true regarding breech presentation,<sup>1</sup> but the same is not yet settled with reference to bregma, brow, and shoulder presentations. There has been considerable literature with reference to the role of the membranes. Conclusive proof as to the effect of "premature rupture" of the membranes upon the first stage of labor is not yet available.

In a previous publication, we pointed out that variations in consistency of the cervix and variations in frequency and intensity of the labor pains did have an important bearing on the duration of the first stage. It was quite obvious, however, that other factors must also be

\*Read at the Sixty-sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

In our earlier series, autohemoclysis was performed 15 times, but a death from septicemia influenced us to abandon the procedure, and we have not employed it during the past ten years.

The essayist's mortality, 3 per cent, approximated our own, which is 3.4 per cent for the entire series, but 2.1 per cent in operative cases, since two patients, admitted as emergencies, died before they reached the operating table.

We have encountered but one ovarian and one abdominal pregnancy (probably secondary) in our series.

Gross evidence of endometriosis has been extremely rare in our experience. Histologically it has been reported several times in removed tissues; it is possible that it has been overlooked in some. We did not have time to review all of our pathologic slides but of 62 secured and examined during the past ten years, we found endometriomas in two removed tubes. Of more interest to us was the presence of decidual reactions which we believed were present in 14 specimens. We agree with Novak, however, that the reaction present is usually a "patchy" one, rarely continuous as in the endometrium and often leading to confusion in its interpretation.

DR. ERLE HENRIKSEN, LOS ANGELES, CALIF. (by invitation).—Two statements are often made in regard to the use of the endometrium as an aid in the diagnosis of ectopic pregnancy. These are the following:

1. The decidua-like response without characteristic villi permits the diagnosis of ectopic pregnancy.

2. The absence of a decidual response and the presence of chorionic villi rule out the presence of pregnancy.

The occasional exceptions of which I shall give examples have caused me to lose faith in these rules. Of 11 patients with clinical diagnosis of ectopic pregnancy, 6 were advised to have laparotomy following my report that the uterine curettings revealed decidua without chorionic villi. Four patients were found to have hemorrhagic cysts of the ovary grossly interpreted as being of corpus luteum origin. One patient had an ovarian cyst with a twisted pedicle. One patient refused surgery and was delivered eight months later of a normal child. On the other hand, five of the 11 patients were discharged following my reports that the endometrial responses were not consistent with pregnancy. The patients were later readmitted as surgical emergencies.

We frown upon the use of the peritoneoscope, because it is not the simple instrument or the safe procedure many would have us believe. Its use should be limited to those who not only know the technique of insertion but can also interpret what they see. Cul-de-sac puncture is still our procedure of choice when added information is deemed necessary.

Endometrial, cervical, and vaginal biopsies, vaginal smears, and sedimentation rates have been of little value in our hands.

shown<sup>2</sup> that duration of the individual labor pain was not important in affecting the duration of the first stage of labor. There is sufficient variation in labor pains, both with respect to frequency and intensity, as labor progresses that one must select a certain time in the labor on which to base his estimate of effectiveness and then try to apply that judgment to the whole of the labor, or the labor must be considered in several segments according to the type of pain present during each of those segments. The latter method is probably too complicated for practical use: The relative infrequency and lack of intensity of the uterine contractions during the effacement phase of the first stage caused us to think that possibly the labor pains should be judged not during effacement but rather at the beginning of the dilatation phase. We, therefore, took as our standard the frequency and intensity of the pains at the time the cervix was either 2 or 3 cm. dilated. We classified the pains as "good," "fair," or "poor," according to the following plan: Good pains were those which occurred at intervals of three minutes or less and with something more than a very weak intensity. Fair pains were those occurring four or five minutes apart with a fair intensity or at intervals of three minutes or less but with a very weak intensity. Poor pains were those occurring at intervals of five or more minutes *and* with a very weak intensity.

#### ANALYSIS OF RECORDS

What might be called completely favorable conditions at the onset of labor would be complete effacement, engagement, soft cervix, and good pains. One hundred thirteen primiparas were in this classification (Table I).

TABLE I. LENGTH OF FIRST STAGE (PRIMIPARAS)

No unfavorable factor  
Effaced, engaged, soft cervix, good pains  
113 patients—Ave. 3 hr. 17 min.  
Range—20 min. to 6 hr. 15 min.

0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
110	3	0	0	0

The average length of the first stage in this group was three hours and seventeen minutes. The shortest was twenty minutes and the longest six hours and fifteen minutes. There were included in this group a small number of patients who had considerable dilatation (four or more centimeters) at the onset of labor. These patients accounted for the very short labors. The majority of patients in this group were in the first stage between two and four hours. It should be noted that no instance of anything like a prolongation of the first stage was noted in this group. A period of about three hours then may be taken as the "basic" duration of the first stage in primiparas.\*†

\*The scientifically accurate time is perhaps three hours and twenty minutes. This figure is a little more difficult to remember and, as will be developed presently, might be a little more difficult to handle in everyday work. The three-hour period is sufficiently close to be satisfactory for practical purposes.

†Eight patients had a "mushy soft" ("1" on our scale) cervix but their first stage of labor averaged two hours thirty-one minutes, not much less than the average for a "2" cervix.

involved. These two variants alone (as analyzed at that time) could not explain either the very short or the very long labors. It gradually became obvious to us that we could not learn what these other factors were without careful examination of a considerable series of patients at the onset of labor and close observation of changing conditions throughout the labor. To see for the first time a patient who has already been in labor several hours does not give us the necessary information as to the conditions present at the time of the onset of the pains and, therefore, leaves us unable to judge what total of work is presented to the uterine forces. In the past few years, we have been making an effort, therefore, to see more patients as their labors begin and to note the relative degree of effacement of the cervix, as well as the dilatation of the external os, the consistency of the cervix, and the station of the presenting point. Balancing this information with the character of the labor pains subsequently observed, we are now able to account for most, if not all, of the variations involved in the first stage. We find ourselves able to predict the duration of the first stage quite accurately. The occasional exceptions can usually be traced to definite pathology.

It should be pointed out that the patient must be seen at the onset of labor. We have found that an examination made the day previous to the onset of labor is not reliable, as in a considerable number of patients quite marked changes take place in the last twenty-four hours before labor begins. We have at present available for study 676 primiparas and 374 multiparas who were seen at the onset of their labors or very shortly thereafter. In a few instances, the primiparas were seen as much as one and one-half (or two) hours after the onset when the uterine contractions had been very weak and infrequent, and it was obvious that no material change had yet taken place. No multipara was included in this group when more than one hour had elapsed since the first discomfort was experienced. These are consecutive cases with no selection or elimination. (A much larger series of patients would have been desirable to prove the thesis to follow, but the conclusions are so clear-cut and the information so readily usable by physicians and students alike that it seemed wise to present the material now.)

#### DEFINITIONS

Effacement was said to be present (for purposes of this study) when the cervix was either completely effaced or was three or more centimeters dilated (even though there might still be a considerable thickness to the cervical wall). All lesser degrees of effacement were said to be "not effaced."

If the presenting point was at or below the level of the ischial spines, the head was said to be "engaged;" if the presenting point was at any higher level, it was said to be "not engaged."

If the cervix was of the consistency of one's lip, or softer, we called it a "2" cervix; if of the consistency of the ala of the nose, or firmer, we called it a "3" cervix.

In judging the effectiveness of labor pains, we considered intensity and frequency. We did not consider duration as we had previously



TABLE V. LENGTH OF FIRST STAGE. EFFECT OF "3" CERVIX

<i>Primiparas</i>		
Not effaced, not engaged, "2" cervix, good pains		6:27
Not effaced, not engaged, "3" cervix, good pains		9:19
<i>Multiparas</i>		
Not effaced, not engaged, "2" cervix, fair pains		6:31
Not effaced, not engaged, "3" cervix, fair pains		8:47

Fair pains (Table VI) likewise require three hours more to dilate the cervix in primiparas and two hours more in multiparas.

Poor pains, on the other hand (Table VII), constitute a more potent factor and, instead of adding three hours to the length of labor when the pains are good, we must add three times three for primiparas and three times two for multiparas.\*

TABLE VI. LENGTH OF FIRST STAGE. EFFECT OF "FAIR" PAINS

<i>Primiparas</i>		
Not effaced, engaged, "2" cervix, good pains		6:04
Not effaced, engaged, "2" cervix, fair pains		9:33
<i>Multiparas</i>		
Not effaced, engaged, "2" cervix, good pains		3:19
Not effaced, engaged, "2" cervix, fair pains		5:19

TABLE VII. LENGTH OF FIRST STAGE. EFFECT OF "POOR" PAINS

<i>Primiparas</i>		
Not effaced, engaged, "2" cervix, good pains		6:04
Not effaced, engaged, "2" cervix, poor pains		15:08
<i>Multiparas</i>		
Not effaced, engaged, "2" cervix, good pains		3:19
Not effaced, engaged, "2" cervix, poor pains		9:56

TABLE VIII. LENGTH OF FIRST STAGE. EFFECT OF HIGH STATION

<i>Primiparas</i>		
Effaced, engaged, "2" cervix, good pains		3:32
Effaced, not engaged, "2" cervix, good pains		4:45
<i>Multiparas</i>		
Effaced, engaged, "2" cervix, good pains		1:43
Effaced, not engaged, "2" cervix, good pains		2:34

Lack of engagement is a matter of less importance and apparently affects primiparas and multiparas to the same degree, as we need add only one hour in each group (Table VIII).

Those primiparas having one unfavorable factor are summarized in Table IX. There were 59 patients whose cervixes were not effaced but in whom engagement was present, cervix soft, and pains good. The average for this group was predicted to be six hours and was computed at

\*Further classes of "very poor" and "very, very poor" pains will be possible in a sufficiently large series. A few such patients in this present series materially increased the averages in the "poor pains" groups in Tables XV, XVII, XIX, and XX.

TABLE II. LENGTH OF FIRST STAGE (MULTIPARAS)

No unfavorable factor  
 Effaced, engaged, "2" cervix, good pains  
 53 patients—Ave. 1 hr. 43 min.  
 Range—5 min. to 5 hr. 35 min.

0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
53	0	0	0	0

Table II shows the similar data for the 53 multiparas in this classification. The usual duration of the first stage in this group is very close to two hours. The average of one hour and forty-three minutes is slightly less, due to the fact that several of these patients also had considerable dilatation at the onset of labor and the average of the whole group was thereby reduced. The "basic" duration of the first stage in multiparas is then about two hours, and the "basic difference" between a primipara and multipara is about one hour.

In the remaining 563 primiparas (83 per cent) and 321 multiparas (86 per cent), one or more of the above four factors (effacement, engagement, consistency of cervix, character of pains) was found to be unfavorable; and the labor, thereby, prolonged beyond the basic three hours for primiparas and basic two hours for multiparas. If two factors were unfavorable, further lengthening of the first stage was observed; three or more unfavorable factors caused a further increase, etc. Carrying this analysis to the limit of the possibilities involved, we were able to develop a table whereby the length of any labor can be predicted with a considerable degree of accuracy.

Lack of effacement adds three hours in primiparas and two hours in multiparas, the same length of time as the basic figures for these two groups (Table IV).

A slightly firmer ("3") cervix also adds three hours (Table V) for primiparas and two hours for multiparas.

TABLE III. PREDICTING THE LENGTH OF FIRST STAGE

		PRIMIPARAS	MULTIPARAS
Effaced	{	Good pains	3 hr.
Engaged		Fair pains	2 hr.
"2" Cervix		Poor pains	4 hr.
Effaced	{	Good pains	12 hr.
Engaged		Fair pains	8 hr.
"3" Cervix		Poor pains	4 hr.
			6 hr.
			10 hr.
If not effaced add		3 hr.	2 hr.
If not engaged add		1 hr.	1 hr.

TABLE IV. LENGTH OF FIRST STAGE. EFFECT OF NONEFFACEMENT

<i>Primiparas</i>	
Effaced, engaged, "2" cervix, fair pains	6:56
Not effaced, engaged, "2" cervix, fair pains	9:33
<i>Multiparas</i>	
Effaced, engaged, "2" cervix, good pains	1:43
Not effaced, engaged, "2" cervix, good pains	3:19

Table XI shows primiparas with two unfavorable factors. The computed and predicted figures are again found to check very closely in each subgroup of patients. In this whole group there were 13 patients with labors of between twelve and eighteen hours and one patient in excess of eighteen hours. Multiplication of unfavorable factors may at times prolong the labor beyond the predicted level. Nevertheless, when it is considered that 143 of these 157 patients had short, or relatively short, labors, the reliability of the index is apparent.

The same data for multiparas (Table XII) show 137 of 139 patients under twelve hours and again a very close reliability of prediction for each subgroup.

TABLE XII. LENGTH OF FIRST STAGE (MULTIPARAS)

## Two unfavorable factors

			(Predicted)	
Not effaced, not engaged	81 patients	4:16	5 hr.	
Not effaced, "3" cervix	5 patients	5:28	6 hr.	
Not effaced, fair pains	17 patients	5:27	6 hr.	
Not engaged, "3" cervix	9 patients	3:15	4 hr.	
Not engaged, fair pains	26 patients	5:20	5 hr.	
"3" cervix, fair pains	1 patient	4:00	5 hr.	

0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
107	30	2	0	0

When three unfavorable factors are present (Table XIII for primiparas and Table XIV for multiparas), the prediction for each individual patient becomes somewhat less exact although for any considerable group of patients the prediction is still very accurate. Sixty-nine patients whose cervixes were not effaced and presenting part not engaged and with only fair pains had a predicted duration of ten hours and a computed duration of ten hours and one minute. Two primiparas in this

TABLE XIII. LENGTH OF FIRST STAGE (PRIMIPARAS)

## Three unfavorable factors

			(Predicted)	
Not effaced, not engaged, "3" cervix	33 patients	9:19	10 hr.	
Not effaced, not engaged, fair pains	69 patients	10:01	10 hr.	
Not effaced, "3" cervix, fair pains	10 patients	10:52	12 hr.	
Not engaged, "3" cervix, fair pains	15 patients	8:30	10 hr.	
Poor pains	16 patients	12:29	12 hr.	

0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
28	81	24	8	2

TABLE XIV. LENGTH OF FIRST STAGE (MULTIPARAS)

## Three unfavorable factors

			(Predicted)	
Not effaced, not engaged, "3" cervix	6 patients	6:12	6 hr.	
Not effaced, not engaged, fair pains	32 patients	6:31	7 hr.	
Not effaced, "3" cervix, fair pains	1 patient	6:10	8 hr.	
Not engaged, "3" cervix, fair pains	0		6 hr.	
Poor pains	9 patients	7:24	8 hr.	

0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
24	21	3	0	0

TABLE IX. LENGTH OF FIRST STAGE (PRIMIPARAS)

One unfavorable factor			(Predicted)
Not effaced	59 patients	5:59	6 hr.
Not engaged	41 patients	4:23	4 hr.
No soft cervix	17 patients	5:52	6 hr.
Fair pains	30 patients	6:44	6 hr.

0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
94	53	0	0	0

five hours and fifty-nine minutes. There were 30 patients whose cervix was effaced and soft and where the head was engaged but who had only fair pains. The predicted duration of the first stage in this group was six hours and the average found to be six hours and forty-four minutes. Seventeen patients had a firmer cervix but all other conditions were favorable. These "six-hour" patients averaged five hours and fifty-two minutes. Forty-one patients entered labor with the fetal head high but all other conditions favorable, including good pains. The predicted duration for this group was four hours and the average was found to be four hours and twenty-three minutes. It should be noted that there was no instance of a first stage of more than twelve hours in any of these four subgroups. About two-thirds of all these patients had labors of less than six hours and one-third between six and twelve hours.

TABLE X. LENGTH OF FIRST STAGE (MULTIPARAS)

One unfavorable factor			(Predicted)
Not effaced	16 patients	3:19	4 hr.
Not engaged	49 patients	2:34	3 hr.
"3" cervix	1 patient	2:40	3 hr.
"Fair" pains	11 patients	3:41	4 hr.

0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
75	2	0	0	0

Table X shows the similar figures for multiparas.\* Only 2 of 77 patients in these four subgroups had a first stage in excess of six hours. The predicted and computed figures are quite close, considering the small number of patients involved.

TABLE XI. LENGTH OF FIRST STAGE (PRIMIPARAS)

Two unfavorable factors			(Predicted)
Not effaced, not engaged	67 patients	6:27	7 hr.
Not effaced, "3" cervix	12 patients	8:51	9 hr.
Not effaced, fair pains	28 patients	8:49	9 hr.
Not engaged, "3" cervix	17 patients	6:39	7 hr.
Not engaged, fair pains	26 patients	7:41	7 hr.
"3" cervix, fair pains	7 patients	11:56†	9 hr.

0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
64	79	13	1	0

†Two of these patients had an unusually firm cervix, 16 and 17 hours, respectively.

\*In multiparas where the cervix is effaced, relative firmness ("3") of the cervix apparently causes only about one hour increase. Where the cervix is not effaced, the difference is the usual "basic" two hours.

Six unfavorable factors (Tables XIX and XX) show for primiparas a labor in excess of twenty-four hours to be the rule and therefore normal. There were no labors less than twelve hours. The one multipara whose labor was less than six hours probably represents an error in the initial recordings on this patient.

TABLE XIX. LENGTH OF FIRST STAGE (PRIMIPARAS)

Six unfavorable factors

Not effaced, not engaged, "3" cervix, poor pains				(Predicted) 19 hr.
16 patients      29:37				
0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
0	0	5	2	9

TABLE XX. LENGTH OF FIRST STAGE (MULTIPARAS)

Six unfavorable factors

Not effaced, not engaged, "3" cervix, poor pains				(Predicted) 13 hr.
9 patients      13:57				
0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
1	2	5	1	0

## DISCUSSION

It should be noted that the management of this series of patients did not include heavy sedation for any first stage. Nitrous oxide oxygen with small doses of morphine (on indication only) were the only means of sedation employed. Other patients delivered in the hospital during the same period and to whom heavy sedation was given had much longer labors. One patient only was excluded from this series because of a pathologically hard cervix. In one patient only a small pelvis might have had a deterrent effect on the course of the labor. This patient was a multipara for whom a thirteen-hour labor was predicted, and she was not completely dilated until the end of seventeen hours. Her conjugata vera was estimated at 8.5 cm. Whenever a patient developed a secondary inertia with no pains for a period of several hours, that painless period was not counted in the total duration of her labor. The number of induced labors was too small for us to tell whether the induced labors were either shorter or longer than those occurring spontaneously. The same can be said with respect to premature rupture of the membranes.

## SUMMARY

Table XXI shows in simple form a method for predicting the duration of the first stage of labor with the percentage likelihood of the occurrence of "good," "fair," and "poor" pains so that, with any given patient, the likely duration can be quite readily determined even in advance of any labor pains. As soon as the first dilating pains appear, the patient can be completely catalogued and the time of complete dilatation readily determined.

This knowledge is of importance in several ways. If a long labor can be predicted, the need of maintenance of free food and fluid intake is

whole group (represented by Table XIII) had a first stage in excess of twenty-four hours, the first instances of what might be called "prolonged labor." Thus, a labor in excess of twenty-four hours may be considered distinctly abnormal unless at least three unfavorable factors are present in the patient.

Four unfavorable factors bring the primiparas' labor up to thirteen to fifteen hours (Table XV) and multiparas' labor to nine to ten hours (Table XVI). Short labors have now become quite uncommon, and there were five primiparas whose labors exceeded twenty-four hours.

TABLE XV. LENGTH OF FIRST STAGE (PRIMIPARAS)

Four unfavorable factors				(Predicted)
Not effaced, not engaged				
"3" cervix, fair pains	26 patients	15:00		13 hr.
Not effaced, poor pains	12 patients	17:25		15 hr.
Not engaged, poor pains	16 patients	11:31		13 hr.
"3" cervix, poor pains	7 patients	13:49		15 hr.
0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
3	19	27	7	5

TABLE XVI. LENGTH OF FIRST STAGE (MULTIPARAS)

Four unfavorable factors				(Predicted)
Not effaced, not engaged,				
"3" cervix, fair pains	14 patients	8:47		9 hr.
Not effaced, poor pains	9 patients	9:56		10 hr.
Not engaged, poor pains	12 patients	9:00		9 hr.
"3" cervix, poor pains	0 patients			9 hr.
0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
9	18	7	1	0

Five unfavorable factors (Tables XVII and XVIII) show a disappearance of the short labors (six hours) for both primiparas and multiparas, and an appearance of an appreciable proportion of primiparas in excess of twenty-four hours.

TABLE XVII. LENGTH OF FIRST STAGE (PRIMIPARAS)

Five unfavorable factors				(Predicted)
Not effaced, not engaged, poor pains	25 patients	23:00		16 hr.
Not effaced, "3" cervix, poor pains	7 patients	24:53		18 hr.
Not engaged, "3" cervix, poor pains	7 patients	17:46		16 hr.
0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
0	6	12	12	9

TABLE XVIII. LENGTH OF FIRST STAGE (MULTIPARAS)

Five unfavorable factors				(Predicted)
Not effaced, not engaged, poor pains	12 patients	11:48		11 hr.
Not effaced, "3" cervix, poor pains	0 patients			12 hr.
Not engaged, "3" cervix, poor pains	0 patients			10 hr.
0-6 HR.	6-12 HR.	12-18 HR.	18-24 HR.	OVER 24 HR.
0	4	6	2	0

Dr. Calkins has brought out a very interesting method by which we may predict with some satisfaction the duration of the first stage of labor. As we all know that is the stage during which the family are requesting that something be done for the patient. With too much urging very frequently intervention is undertaken which may be harmful both to the mother and child. With this knowledge we might be more able to pacify them.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—After having read the paper and heard it presented this morning I feel that there is considerable practical value in it, and one of the very sensible things is keeping up the spirits of the patient during a period that is not always predictable. If Dr. Calkins has the formula that will give us some information, we may be able to do more for our patients. I hope he will keep on with this study and give us a formula for the second stage so that we may pacify not only the patient but the family as well.

I wonder how much the question of sedation is going to enter into this. Dr. Calkins has plainly indicated he feels that in some patients sedation will prolong the duration of labor. I think there would be great difficulty, however, in convincing the public and the patient sufficiently so that it would lead to an elimination of sedative measures. These academic questions constitute one of the important problems to which the obstetrician should pay attention and attempt to solve.

DR. G. D. ROYSTON, ST. LOUIS, MO.—I would like to ask whether these observations were made personally by Dr. Calkins or by one of his subordinates?

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—The labor was definitely prolonged where sedatives were used. At what stage was the sedation first begun?

DR. NORMAN R. KRETZSCHMAR, ANN ARBOR, MICH.—I would like to ask Dr. Calkins to explain when and how he evaluates the pains. From the subjective reaction of the patient, one never knows when she is having a good pain nor does palpation seem to give definite evidence of the quality of the pains.

DR. NORMAN HARRIS WILLIAMS, BEVERLY HILLS, CALIF. (by invitation).—What is Dr. Calkins' definition of the termination of the first stage of labor?

DR. J. MALDONADO, SANTE FE, N. M. (by invitation).—I would like to ask what effect the presenting part has on the pains?

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—Are the dilatation and the consistency of the cervix based on rectal or vaginal examination?

DR. CALKINS (closing).—Dr. Goldsborough asked at what time we estimated the efficiency of the labor pains. The answer is, just as soon as we know the cervix is beginning to dilate. We have to wait until it is 2 or 3 cm. dilated because we wish to estimate the pains during the dilatation phase and not during the effacement phase. Labor begins whenever the patient experiences her first discomfort.

Dr. Royston asked by whom the observations were made. A small proportion were made by myself, the majority by my resident, and a few by my intern. My senior students can make these observations just as accurately and predict the labors just as satisfactorily as we indicated in this paper.

Dr. Schwarz asked at what time those few patients had received their heavy sedation. In most instances at a dilatation of about 4 to 6 cm.

Dr. Kretzschmar asked about the evaluation of pains with relation to their intensity. Of course, the method we used is very crude but it seems to work. If we can depress the uterine wall very markedly during the contraction, that contraction is very weak. If we can depress it moderately, that is a fair contraction; if not at all, it is a very firm contraction. That is the only method we employ and we think that it is all that is necessary. It must be taken, however, in conjunction with the frequency of the pains. One or the other alone is not sufficient.

TABLE XXI. PREDICTING THE LENGTH OF FIRST STAGE

		PRIMIPARAS	MULTIPARAS
Effaced Engaged "2" Cervix	Good pains 63%	3 hr.	2 hr.
	Fair pains 25%	6 hr.	4 hr.
	Poor pains 12%	12 hr.	8 hr.
Effaced Engaged "3" Cervix	Good pains 45%	6 hr.	4 hr.
	Fair pains 33+	9 hr.	6 hr.
	Poor pains 22%	15 hr.	10 hr.
If not effaced add		3 hr.	2 hr.
If not engaged add		1 hr.	1 hr.

obvious. If a short, easy labor can be predicted, the need for operative intervention in certain types of pathology is obviated. It is high time that labors should be judged on the anatomic and physiologic factors in the genital tract rather than on "manufactured diets" as age and stature of the whole body. It is also important, if the labor goes definitely beyond the predicted limits, that careful search for unrecognized abnormalities should be instituted without delay.

Finally, it is interesting to speculate on the etiology of the variations in the cervix and in the uterine contractions. The cause is not anatomic; it is almost certainly physiologic. There is some evidence that variation in the cervix may produce variation in the uterine contractions and vice versa. The etiology of the onset of labor is inextricably involved in both. Further research is obviously necessary. Only when we find this physiologic factor can we hope to so "prepare" the least favorable patients in advance that they may enter labor with unresisting cervixes and good uterine contractions.

#### REFERENCES

- (1) *Calkins, L. A., Litzenberg, J. C., and Plass, E. D.*: AM. J. OBST. & GYNEC. 22: 604, 1931. (2) *Calkins, L. A.*: Ibid. 27: 349, 1934. (3) *Calkins, L. A., Irvine, J. H., and Horsley, G. W.*: Ibid. 19: 294, 1930.

1010 MEDICAL ARTS BUILDING

#### DISCUSSION

DR. FRANCIS C. GOLDSBOROUGH, BUFFALO, N. Y.—One or two points Dr. Calkins has emphasized are quite important. (1) The position of the child plays very little part in the way in which the cervix dilates. (2) It is important to see the patient as soon as the pain begins. We too frequently see her only after she has been in labor for a few hours and there is some effacement and some dilatation. One of the main points Dr. Calkins brought out is that we should know the condition of the cervix when labor starts in order to gauge progress.

I am a little uncertain as to what is Dr. Calkins' definition of the onset of labor. It seems to me the average duration of his first stage is rather shorter than most of us have been led to accept, and I am wondering whether he sets the onset of labor as the time when the cervix is effaced or when the patient first complains of painful contractions of the uterus?



## VARIABLE SIGNIFICANCE OF HEARTBURN\*

NORMAN H. WILLIAMS, M.D., BEVERLY HILLS, CALIF.

OF ITSELF the frequency of heartburn during pregnancy gives distinction to the ailment. Never serious as a threat to health, even a mild degree of heartburn, if persistent, will lower personal efficiency in meeting the responsibilities of daily life; while intense heartburn at night will banish sleep completely. Of these consequences prospective mothers complain, and from them ask relief. Household remedies may suffice; but not always. Indeed, intractable cases continue to baffle physicians. And logically enough, members of the medical profession from time to time delve into the problem clinically and experimentally seeking the cause for and the cure of this annoyance common among both men and women; and especially likely to occur during pregnancy.

### INCIDENCE

Some degree of heartburn, slight or severe, is associated with two-thirds of the cases of pregnancy, irrespective of the age or parity of the subjects. It makes its appearance at any time during the period of gestation. In a statistical survey, Rodway and Shelley noted the following distribution of the cases they observed: 15.1 per cent during the first four months of pregnancy, 20.2 per cent in the fifth month, 45.5 per cent between the sixth and eighth months, 18.2 per cent in the ninth month. Most intense during the later months the discomfort was often described as torture.

### CAUSATION

High-strung individuals are predisposed to heartburn. But those who have a placid temperament experience it notably when under mental strain. It has been called "the student's disease," because so often it is the penalty of consistent mental concentration. There incidentally lies a hint of the nervous factor concerned.

Diet, too, plays a role, well defined, if not leading. Drinking water in suitable amounts, avoiding sweets, pastry, fatty food, and acid beverages are believed to be preventive measures; while milk and the use in general of a high protein diet have been recommended as curative.

Gastric hyperacidity was accepted for a long time as the explanation for the ailment. Accordingly pregnancy, it was assumed, promoted the secretion of hydrochloric acid excessively; an interpretation that had clinical support. Each of us, not unlikely, has witnessed the grateful attitude of patients advised to counteract what was thought to be gastric hyperacidity by neutralization with an alkali, salts of sodium, magnesium, or aluminium. To the rule, however, there were notable

\*Read, by invitation, at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

Dr. Williams asked when we consider the first stage terminated. When we can no longer feel the cervix. If it is within reach of our rectal examining finger, we feel that it still can be holding the presenting part and the first stage is not over. When it has completely retracted we consider the first stage completed.

Dr. Maldonado asked what effect the presenting part may have on the pain. It was stated in a previous paper to have had no effect whatever in the first stage.

In answer to Dr. Dieckmann, 97 per cent of our examinations were rectal. A vaginal examination is done whenever we feel that the information is incomplete or otherwise unsatisfactory.

Subsequent experiments demonstrated that the sensation in question could be reproduced by the introduction of fluids poured into the esophagus through a catheter. And, amazing fact, the composition of the fluid did not matter. What counted was the irritation of the esophageal mucous membrane, a reaction elicited by bland solutions, even warm or cold water. Specifically, the following materials caused heartburn: Cold water in eight experiments, warm water in three, N/10 HCl in five, N/10 NaOH in six, barium sulfate in one, the subject's own gastric juice in two.

Jones's observations warranted conclusions with respect to heartburn which may be summarized briefly. The chemical composition of the fluids concerned is of less importance than their quantity and the rapidity with which they are introduced into the esophagus. Constriction of the cardiac sphincter, exquisitely demonstrable when barium solution is used, prevents passage of the material. This inhibition is followed by waves of reverse peristalsis which carry the fluid upward. Furthermore, coincident with the disappearance of retroperistaltic waves the discomfort ceases. Accordingly for the relief of heartburn, the administration of atropin to relax the neuromuscular mechanism involved represents a logical type of treatment.

#### GASTRIC CHANGES INCIDENT TO PREGNANCY

We must examine next the physiologic changes resulting from the influence of pregnancy upon the gastrointestinal tract. Current methods of investigation have clarified at least three cardinal facts, namely, changes in the position, in the musculature, and in the motility of the stomach.

Normally the stomach is in a vertical position, the lesser curvature to the right approximately parallel with the spinal column and the cardia opposite the tenth dorsal vertebra. The alterations consequent upon pregnancy plainly depicted in the diagrams of Hansen have been verified by our own radioscopic studies. As would be expected, the encroachment of the pregnant uterus upon territory formerly occupied by other abdominal organs slowly increases until near term when the topographic transformation becomes maximal. Then the fundus of the stomach has been pushed upward into the left diaphragmatic cup. Simultaneously the axis of the stomach has been rotated to the right approximately 45 degrees. Also the greater curvature has approached the cardia. This horizontal position hinders the stomach in emptying itself.

Added to the changes in the position is atony of the stomach musculature which allows the organ to lie flaccidly against the enlarging uterus. This atony affects the cardiac sphincter and often the esophagus as well, which may permit hiatus herniation. Access of gastric juice to the lower esophagus is thereby favored. Clinically this explains why many patients complaining of heartburn discover the symptoms exaggerated when the body posture is recumbent or when effort is made to sit up from the reclining position. Fetal movements, too, may produce this discomfort.

Diminished motility of the stomach is a constant physiologic condition in pregnancy. Normal persons, according to Guthman, have an emptying time of two hours, whereas during pregnancy Hansen found this

exceptions, and sceptics of alkali therapy multiplied after Kehrer in 1905 announced that both combined and free hydrochloric acid are actually below normal in the gastric secretion of pregnant women. Ample confirmation of his analyses has come from many laboratories. An admirable study made by Strauss and Castle in this country contributes substantially to the chemistry involved. Now, it has been established that gastric acidity decreases as pregnancy advances, being lowest in the third trimester when heartburn becomes most prevalent and severe. Following the act of birth, along with the disappearance of heartburn, gastric acidity mounts and its height may treble that of the ante-partum level.

Chemical analysis of the gastric juice inevitably shook the foundation of alkaline therapy, encouraged accurate definition of the secretion by quantitative methods and pointed to the use of hydrochloric acid in cases of heartburn. Promptly the reports of Mason and others proclaimed the relief during pregnancy by this treatment. But before long the need for discrimination was emphasized in recommending any form of medication to alter gastric acidity.

For example Rayner in 1933 recognized three groups in a series of 45 pregnant women suffering from intractable heartburn; first, those who were relieved by acids; second, those who were relieved by alkalis; and third, those in whom the symptom was aggravated by acid and was not relieved by alkali. Similarly Rodway and Shelley two years later in the course of forty gastric analyses upon pregnant women found a low or moderate degree of acidity in twenty-four, and a high degree only in three instances.

It is pertinent that these investigators noted the eventual development of a toxemia in 7.5 per cent of the women who earlier had complained of heartburn. That association encouraged some obstetricians to employ a salt-free diet routinely whenever heartburn became a major complaint. The results were not uniform, as would be expected now that we understand the basis of the disturbance not to be chemical but mechanical, an upset in gastrointestinal dynamics.

#### IMPAIRMENT OF NEUROMUSCULAR MECHANISM

Experimenting with a technique previously employed by Bloomfield and others, Chester Jones localized a number of pathologic manifestations pertaining to the gastrointestinal tract.

He learned that heartburn is derived from spasm of the cardiac sphincter of the esophagus. This was proved by the manipulation of a small distensible balloon attached to a fine rubber tube which was swallowed by subjects of the experiments. The bag's position was followed downward step by step from esophagus to rectum with the help of fluoroscopy. Symptoms caused by pressure of the balloon, inflated at intervals, were accurately localized. The initial observation identified the lower end of the esophagus as the area responsible for heartburn. The pressure of the balloon against the area caused the sensation of burning. "In a few instances the subjects felt as if something sour or hot was being carried upward toward the mouth, simulating the symptom, acid regurgitation."

conclusion, of course, represents no novelty, for Chester Jones and others have convinced most of us, at least, that heartburn is essentially a neuromuscular phenomenon.

Granted this premise and assuming the mechanism to a degree analogous to disturbed intestinal tone in certain postoperative cases, it seemed that the use of prostigmin would have a rational basis as a therapeutic means of relieving the symptom. Accordingly injection of 1 c.c. of 1:2,000 of prostigmin was tried, cautiously, to be sure, until certain it was safe to use the drug in the course of pregnancy. The limited number of our observations does not permit an unqualified conclusion. The results, however, are sufficiently noteworthy to suggest a need for further trial.

Among 16 patients with severe heartburn treated with a single dose of prostigmin one was not benefited, 14 were made comfortable or entirely relieved within twenty-four hours. In about half of these cases the distress gradually recurred in from seven to ten days. A second dose proved as effective as the first. By repetition of the injections these patients were kept free of the symptom with no untoward results.

#### RECAPITULATION

Dietary and other kinds of hygienic indiscretion may provoke heartburn. Sometimes dosage with alkalis affords relief, implying the presence of gastric hyperacidity. Chemical analysis, however, challenged the correctness of that interpretation since it showed hypoacidity more often than not, occasionally complete anaecidity of the stomach contents. Consequently hydrochloric acid has been tried, effectively in some instances.

Whatever the benefits of either alkali or acid therapy, the composition of the gastric juice is not fundamentally at fault. Responsible for the ailment is temporary impairment of the neuromuscular mechanism which controls transportation of the gastric contents.

During pregnancy, the position and motility of the stomach delay the emptying time of this organ, and favor the development of reverse currents that carry material upward. It may reach the esophageal mucous membrane, stimulate contraction of the cardiac sphincter and thus cause heartburn.

With a few exceptions, the hypodermic administration of prostigmin has given relief usually for several days at least. In the event the discomfort recurs this treatment may be repeated.

I wish to acknowledge my indebtedness to Dr. Richard Taylor, radiologist at the Hospital of the Good Samaritan, Los Angeles, California, for the fluoroscopic and x-ray work done in the preparation of this article.

#### REFERENCES

- (1) Barry, D. T.: Irish J. M. Sc. 749, October, 1939. (2) Schmidt, H. W.: Am. J. Digest. Dis. 6: 693, 1939. (3) Evans, J. R., and Bouslog, J. S.: Radiology 34: 530, 1940. (4) Hansen, Rolf: Centralbl. f. Gynäk. 61: 2306, 1937. (5) Winter, E. W.: Centralbl. f. Gynäk. 58: 443, 1934. (6) Winkler, H.: Monatschr. f. Geburtsh. u. Gynäk. 100: 125, 1935. (7) Mason, L. W.: Colorado M. J. 28: 392, 1931. (8) Rodway, Helen E., and Shelley, Orsula: J. Obst. & Gynaec. Brit. Emp. 42: 107, 1935. (9) Brian, Raynor S.: Brit. M. J. 2: 970, 1933. (10) Strauss, M. B., and Castle, Wm. B.: Am. J. M. Sc. 184: 655, 1932. (11) Mann and

period prolonged from fifty to one hundred and thirty minutes. In a few pregnant women the stomach never emptied itself completely. In general, motility decreases directly with the acid content, presumably an explanation for the benefits following the administration of hydrochloric acid, already mentioned. Knowledge to what extent gastric motility depends upon endocrine influence is still wanting. Experimental evidence thus far has been derived only in respect to the thyroid. In their studies Morrison and Feldman have clearly demonstrated a positive relationship between this gland and gastric retention, a relationship independent of the vagus.

With these gestational variations in mind it has seemed reasonable to try to reduce the neuromuscular theory of heartburn, as it may pertain to pregnancy, to factual observations. While investigations are still in progress, they have reached a point where a few conclusions may be expressed with confidence. However, since the work began a number of questions have arisen which cannot be answered at the moment.

#### OBSERVATIONS

We have studied pregnant women by means of x-ray plates and fluoroscopy, both those with and those without heartburn. With the thought of possible damage through repeated x-ray exposures, our observations have been curtailed and the data with respect to a single individual rendered less extensive than final solution of the problem requires. Nonetheless we have already witnessed results with helpful clinical implications.

Initially a 200 c.c. barium meal was given and its propulsion followed through the esophagus. Its behavior in the stomach was watched for a period believed to be within the limits of safety. And, indeed, proved to be so. In these circumstances there was opportunity to note evidences of such phenomena as hiatus hernia, esophageal dilatation, regurgitation, and reverse peristalsis whenever the patient was a victim of heartburn. If not, the observations contributed information relative to the anatomic relations in pregnant women having no digestive complaints, normal cases so to say.

These normal cases left no doubt that the stomach regularly suffered encroachment by its neighbors during pregnancy, was pushed upward to the left and occupied the diaphragmatic cup on that side. No changes appeared in the lower esophagus or cardia, excepting one instance in which there was well-developed hiatus hernia.

Likewise, in seven cases of heartburn, there were no pathologic alterations radioscopically visible. On the other hand in three cases of heartburn there was moderate dilatation of the lower third of the esophagus, in one case the passage of barium was delayed at the cardia with a slight amount of regurgitation, and only in one instance was a hiatus hernia discovered; this, with dilatation above it. Evans and Bousling describe hernia of this type in two cases of intractable heartburn. Such revelations as these imply that the clinical symptom, heartburn, rarely rests upon an anatomic basis and that for the most part its origin and development lie within the domain of pathologic physiology. This

white, private patients. I was able to examine 408 of these carefully for a history of heartburn. I might say that while I ask routinely about nausea, gas, shortness of breath and palpitation of the heart, I do not have heartburn on my questionnaire. Twenty-six of these 408 patients complained of heartburn, or 6.37 per cent. The time in the pregnancy when this complaint occurred was as follows:

Third month	1	Seventh month	5
Fourth month	4	Eighth month	5
Fifth month	3	Ninth month	5
Sixth month	2	Tenth month	1

Since it is possible that those who aborted early or those who were seen only when they came into the hospital for delivery regarded heartburn as too trifling to mention a somewhat false idea of the frequency of this symptom might result. When I selected only those whose course I had personally followed for at least two months, there were 290 patients, 24 of whom complained of heartburn, a percentage of 8.3.

As to the relationship of heartburn to subsequently developing toxemia, my cases showed no serious toxemia. Seven had a systolic blood pressure of as much as 150 on at least one occasion, and two of these showed a trace of albumin in the urine.

The treatment that Dr. Williams suggests, i.e., with prostigmin, seems to me to be a logical one.

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Mann: Am. J. Digest. Dis. 6: 322, 1939. (12) Morrison, S., and Feldman, M.: Am. J. Digest. Dis. 6: 549, 1939. (13) Polley, Howard F.: J. A. M. A. 116: 821, 1941. (14) Slemons, J. M.: West. J. Surg. 48: 7, 1940. (15) Mancini: Chem. Abstract 28: 7362, 1934. (16) Cannon and Roscnbluth: Am. J. Physiol. 119: 285, 1937. (17) Dale, Sir Henry: Chemical Transmission of the Effects of Impulses in the Peripheral Nervous System, Lilly Research Laboratory Dedication, 1935. (18) Jones, Chester M.: Digestive Tract Pain, New York, 1938, The Macmillan Company.

409 NORTH CAMDEN DRIVE

## DISCUSSION

DR. ALEXANDER M. CAMPBELL, GRAND RAPIDS, MICH.—Dr. Williams' statement that the hydrochloric acid in the gastric juice is markedly reduced has been verified by different research workers, but the fact as yet does not seem to be generally recognized by obstetricians. Rodney and Shelley of London investigated 100 cases of heartburn and in only 11 per cent was there a high volume of hydrochloric acid. Yet hyperchlorhydria has usually been considered as the basic cause of heartburn.

The question arises as to what produces the hypochlorhydria of pregnancy, and the relation it has, if any, to heartburn? Castle and Strauss show that in the physiologic anemia of pregnancy, over 50 per cent have a decrease or absence of hydrochloric acid, and that there is a return to normal following parturition. It is estimated that about 50 per cent of pregnant women suffer from a pathologic anemia which suggests that this condition plays a role in the etiology of heartburn.

Sandweiss and his collaborators report that in over 70,000 consecutive admissions of pregnant women to five Detroit Hospitals during a ten-year period, there was only one active case of peptic ulcer, and they suggest that the improvement observed in ulcer during pregnancy may be related to the large amount of A.P.L. hormone present at that time.

Dr. Williams' paper suggests more study of this syndrome which may clarify its etiology and place its management on a scientific basis. It would be of special interest if he continued his research with the dilating balloon to observe what effect prostigmin has on gastric motility in cases of heartburn during pregnancy.

From a long clinical experience in the management of the parturient woman I am of the opinion that in heartburn the neurogenic factor is extremely important and that by a sympathetic, intelligent and painstaking attempt to evaluate all emotional disturbances and all environmental, domestic, and financial maladjustments that much can be done to prevent this disagreeable complication. Until sufficient research work is done to establish the etiologic factors, one can accomplish a great deal by suggestive therapy and a well-balanced liberal diet.

DR. M. PIERCE RUCKER, RICHMOND, VA.—The title of Dr. Williams' paper has been well chosen. Not only has he given us a clinical study of heartburn, but also a very timely study of the physiology of the stomach during pregnancy. Few such studies have been made. Hansen in 1937 showed that toward the end of pregnancy the position of the stomach was markedly changed. It was pushed up into the left dome of the diaphragm, and was rotated some 45 degrees until it lay as a flaccid bag more or less horizontally, on the top of the fundus of the uterus. The tone of the stomach was so much diminished that the emptying time was definitely increased. He did not think that the so-called anemia of pregnancy had anything to do with these changes. One might suppose that progesterin might be the cause of the lessened activity of the stomach, but the recent work of Sleeth and VanLiere would seem to indicate that this hormone has no effect on the emptying time of the stomach.

Not only Hansen but others have shown that there is a tendency to hypoactivity during pregnancy. Dr. Williams has confirmed the findings of Hansen regarding the change in position and tone of the stomach. Any irritation, chemical or mechanical, of the lower end of the esophagus will cause heartburn.

As to the clinical aspects of the presentation, heartburn has not been as impressive a symptom with me as it evidently has been with Dr. Williams. In order to check this, I took at random from my files a number of antepartum records of



In our opinion, the problem is a twofold one: First, is the Walcher position of such established efficiency as to warrant its use in spite of the great distress that it causes the laboring woman; and second, if this efficiency is conceded, is the accepted explanation correct, namely, that an *increase* in the length of the obstetric conjugate is produced?

Walcher originally contended that because of a rotatory movement of the iliac bones against the sacral bone around a transverse axis, the distance from the moving symphysis to the stationary sacral promontory could be increased from 0.8 to 1.3 cm. This statement can easily and accurately be checked by modern roentgen pelvimetry as was suggested by Jareho<sup>15</sup> eleven years ago.

Concerning the theory and the mechanics of Walcher's position, the accepted explanation is that the weight of both legs hanging downward unsupported, pulls on the pelvic ring and produces the maximum possible downward rotation of its anterior half. The sacrum and its promontory, however, are fixed in their position by the counter pull of the spine. These movements in the sacroiliac articulations are favored by the softening of the ligaments which accompanies pregnancy. The exact location of the transverse axis of the rotatory movement has been determined by anatomists<sup>17</sup> as below and posterior to the promontory.

One grave criticism can be levelled against Walcher's conception. Walcher and many of his subsequent supporters measured the diagonal conjugate in the extreme exaggerated lithotomy position "by drawing the knees up as high as possible toward the body," and in the extreme hyperextended position thus comparing the two extremes. Since the purpose of Walcher's position is to facilitate the entrance of the fetal head into the inlet, thus indicating its use during the first and second stage of labor, it is obvious that the extreme lithotomy position need not be considered here, and that logical comparison should be made between the ordinary comfortable dorsal position and the Walcher position. This criticism was first expressed in 1891 by Klein,<sup>17</sup> who proved in his study on cadavers that the *decrease* in the length of the conjugate from the dorsal to the extreme lithotomy position far exceeded the *increase* in the length of the conjugate from the dorsal to the hanging position. This increase was as little as 0.1 cm. in normal, 0.05 cm. in large, and 0.07 cm. in contracted pelves.

Another criticism based upon some fundamental principles in Walcher's position was made by Wahl<sup>29</sup> in 1930, who emphasized the fact that the axis for the sacroiliac rotatory movement is located *below* and *posterior* to the sacral promontory. Some contracted pelves present a prominent promontory with a pronounced sacral excavation. In this group, a downward rotation of the symphysis will theoretically produce some enlargement of the obstetric conjugate. A fairly large group of contracted pelves, however, show a straight, flat sacrum with a prominence at the junction of the first and second sacral vertebrae or lower down. The functioning obstetric conjugate in these cases should be plotted from the symphysis to this sacral prominence rather than to the anatomical promontory. Since this prominence is located below the transverse axis of rotation, a downward tilting of the symphysis will theoretically *shorten* rather than *lengthen* the obstetric conjugate, thus con-

## ROENTGEN PELVIMETRIC ANALYSIS OF WALCHER'S POSITION\*

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THE Walcher position of extreme body hyperextension during labor is recommended in leading textbooks of obstetrics as a useful procedure in aiding the entrance of the fetal head into a moderately narrowed pelvis. Although critical reviews of this procedure have appeared periodically, and most of them have been in accord with Walcher's idea, several experienced obstetricians have voiced contrary opinions.

Even before Walcher's original publication in 1889,<sup>30</sup> Albucasis<sup>6</sup> in 1060 recommended a similar hanging position, as did also Mercurio<sup>6</sup> in 1589 and Melli<sup>6</sup> in 1738. In his original publication, Walcher reported the use of the hyperextended position in 6 patients, in all of whom were noted an increase in length of the diagonal conjugate of from 8 to 13 mm. No additional data were presented in his subsequent presentation ten years later.<sup>31</sup> Since then, a considerable number of reports have appeared and these have been exhaustively reviewed by Jarcho<sup>15</sup> in 1929.

Many authors, including Duehrssen,<sup>9</sup> Kalt,<sup>16</sup> Fehling,<sup>10</sup> Fothergill,<sup>11</sup> Krukenberg,<sup>6</sup> Jarcho<sup>15</sup> and others,<sup>3, 5, 7, 8</sup> have concurred in Walcher's original contention that this position causes a definite increase in the diagonal conjugate, and is therefore, a beneficial procedure. Apparently, all of these authors measured the increase of the diagonal conjugate from the hyperflexed (exaggerated lithotomy position) to the hyperextended (Walcher) position as did Walcher originally.

The present-day textbook opinion is presented as follows: DeLee<sup>6</sup> recommends, as one method of treatment for a moderately contracted pelvis, the use of the Walcher position "in which can be obtained a lengthening of the conjugate of from six to twelve millimeters." Interestingly enough, he also states that he has "curiously obtained as good or better results with the exaggerated lithotomy position." Sellheim,<sup>21</sup> in Halban-Seitz's handbook, states that "in Walcher's position . . . the inlet will be widened in the straight diameter, the outlet narrowed." Titus<sup>28</sup> feels that "additional space may be given during delivery while the head is above the midpelvis with the Walcher position." Williams<sup>33</sup> also teaches that in "contracted pelvis with a conjugate vera of from nine to ten centimeters, if engagement fails to occur after complete dilatation of the cervix, the patient should be placed in the Walcher position. In many cases, this procedure will bring about a sufficient lengthening of the anteroposterior diameter of the superior strait to permit engagement."

\*Read at a meeting of the Chicago Gynecological Society, May 16, 1941.

in the technical arrangements and the positioning of the patient. All exposures, therefore, were made with the patient in a supine position in order to exclude any possible influence resulting from rotating the patient laterally. In addition, this arrangement permitted the position of the cassette holder, the tube-stand, and the target film distance to remain unchanged.

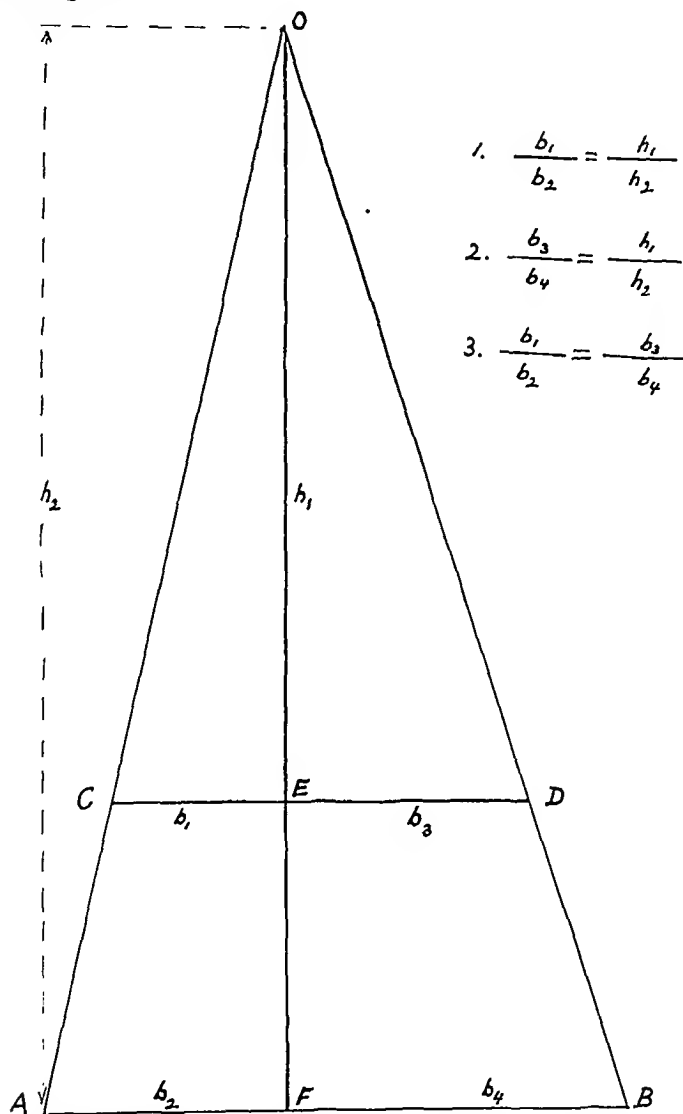


Fig. 3.—Diagram illustrating Euclid's geometrical theorem of the similar triangles in which the altitudes are proportional to their bases.

The patient was placed horizontally in the dorsal position on a cart in front of an upright Potter-Bucky grid with the pelvis directly over the center of the film. The x-ray beam leaving the target horizontally, was directed transversely through the pelvis (Fig. 1). Following the first exposure, the tube stand and Potter-Bucky grid remained unchanged, while the cart was advanced to a point where its caudal edge was approximately at the vertical center line of the Potter-Bucky grid. The patient was then placed in the Walcher position over the edge of the cart and properly centered for the second exposure (Fig. 2). With

traindicating the use of the Walcher position. In such cases, an upward rotation of the anterior half of the pelvic ring as obtained in the lithotomy position will theoretically *lengthen* the functioning conjugate (Figs. 9 and 10). This fact may explain DeLee's statement that

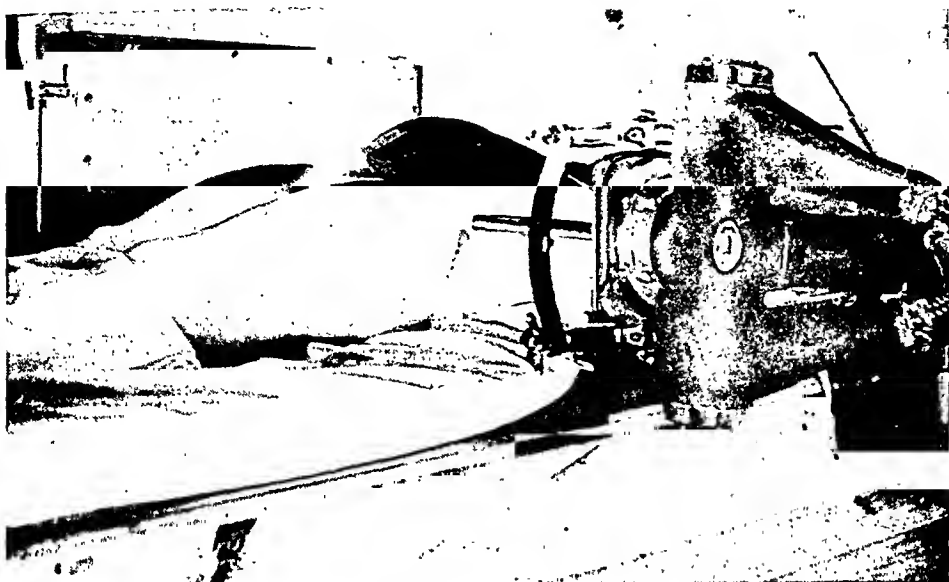


Fig. 1.

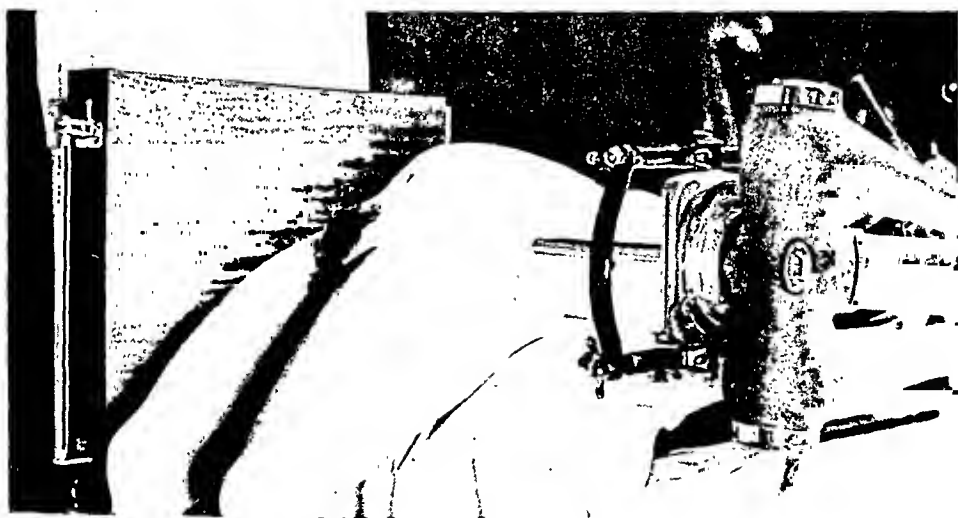


Fig. 2.

Figs. 1 and 2.—Technical setup for taking successive radiographs in dorsal and in Walcher's positions.

he "curiously obtained as good or better results with the exaggerated lithotomy position which is theoretically contraindicated because it is supposed to contract the anteroposterior diameter of the inlet." Wahl,<sup>29</sup> however, did not support his ideas with the use of roentgen pelvimetry.

#### PRESENT STUDY

To obtain the best comparative roentgenographic measurements of the pelvis, we chose a method which reduced to a minimum any changes

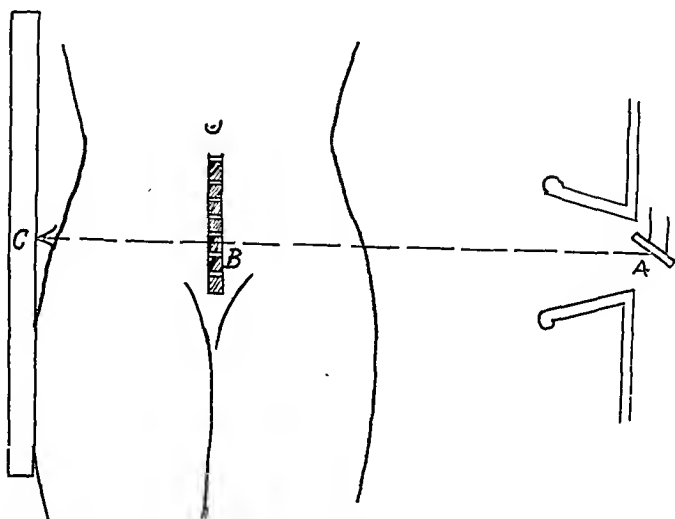


Fig. 5.—Illustrates the simplicity of the process of centration and placement of the metal ruler (B) in the "metal rod method" of roentgen pelvimetry.

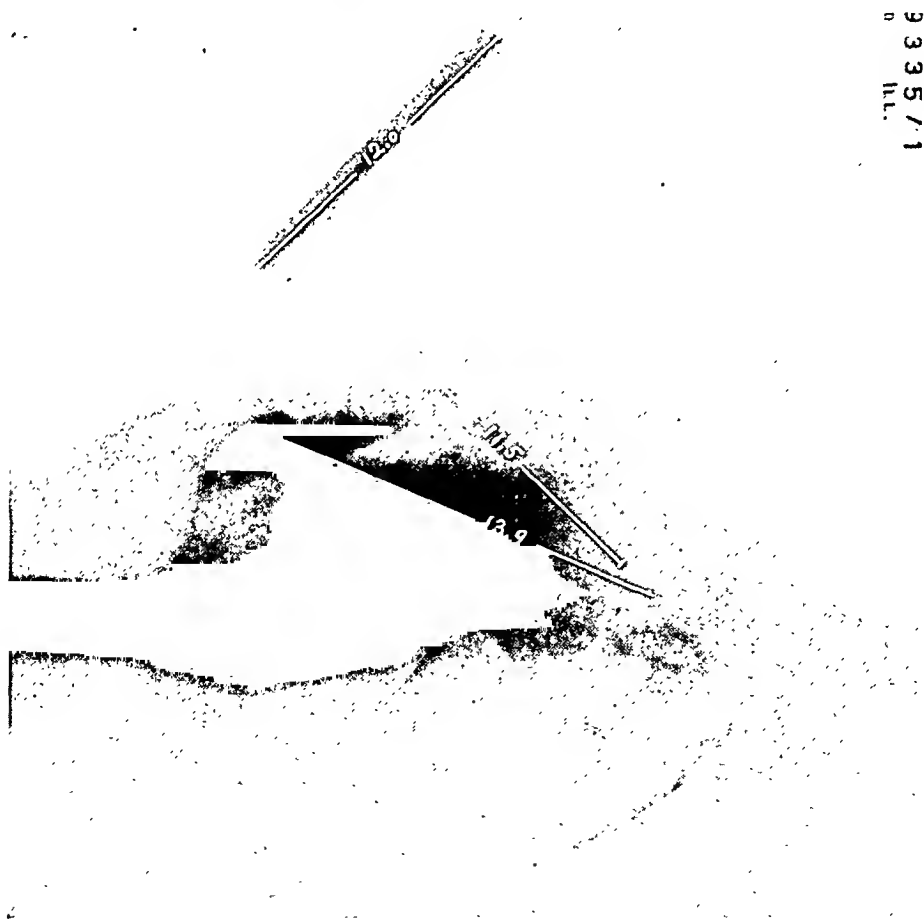


Fig. 6.—Radiogram with pertinent measurements inserted. The equation is  $\frac{x}{13.9} = \frac{10}{12}$ ,  $12X = 139$ ,  $X = 11.6$ . The obstetric conjugate measures 11.6 cm. as calculated herein.

this technique any minor errors would be equally apparent on both films, and therefore, direct, accurate comparison could be made.

To obtain the actual measurements, a 10 cm. metal ruler was placed lengthwise over the lower abdomen of the patient directly over the midline, carefully avoiding any lateral tilting. The shadowgraph of

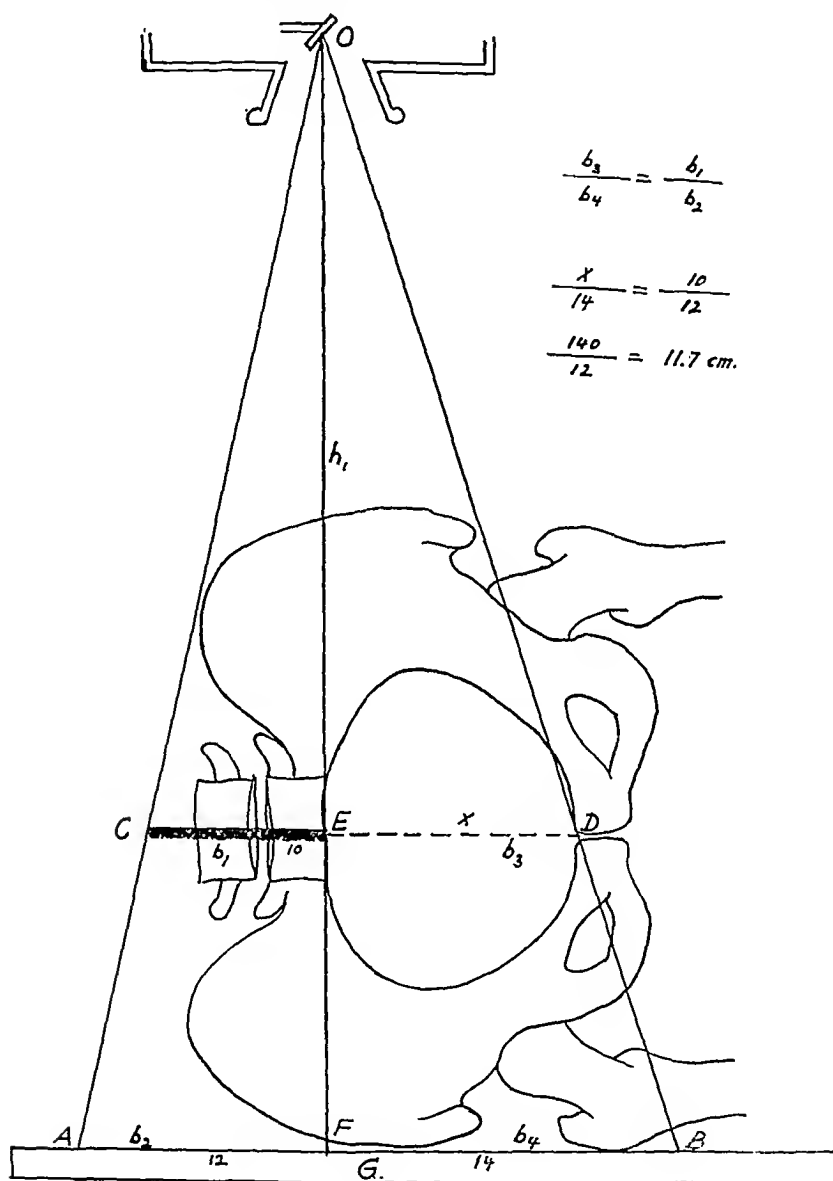


Fig. 4.—Bony pelvis, x-ray tube, film cassette (G), and a metal ruler (C-E) are transposed upon the previous diagram of the similar triangles. The simple equation shown herein may now apply.

the ruler on the film indicated the exact rate of enlargement on each radiograph (Fig. 6). This enlargement is an unavoidable by-product of the central projection in radiographic work.

The underlying principle of this method is based on the geometrical theorem of the "similar triangles" postulated by Euclid, in which the altitudes of two similar triangles are proportional to their bases. In this method of roentgenographic pelvimetry, two pairs of similar tri-

angles are obtained, one with the metal ruler, the other with the obstetric conjugate as the easily identifiable base (Figs. 3 and 4). The first essential condition for the production of these pairs of similar triangles is that their altitudes be exactly identical, and this requires that both the metal ruler and obstetric conjugate be placed at exactly the same distance from the film and target. This is accurately accomplished by placing the ruler over the midline of the patient while lying on her back (Fig. 5). Thus, the metal ruler and the obstetric conjugate

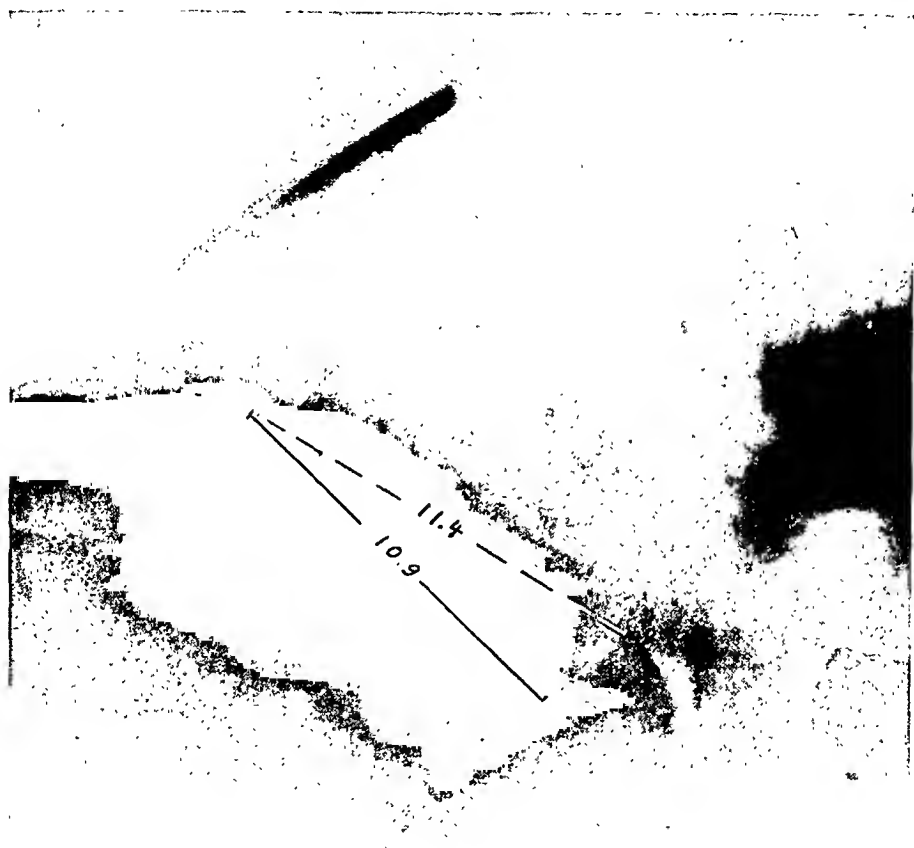


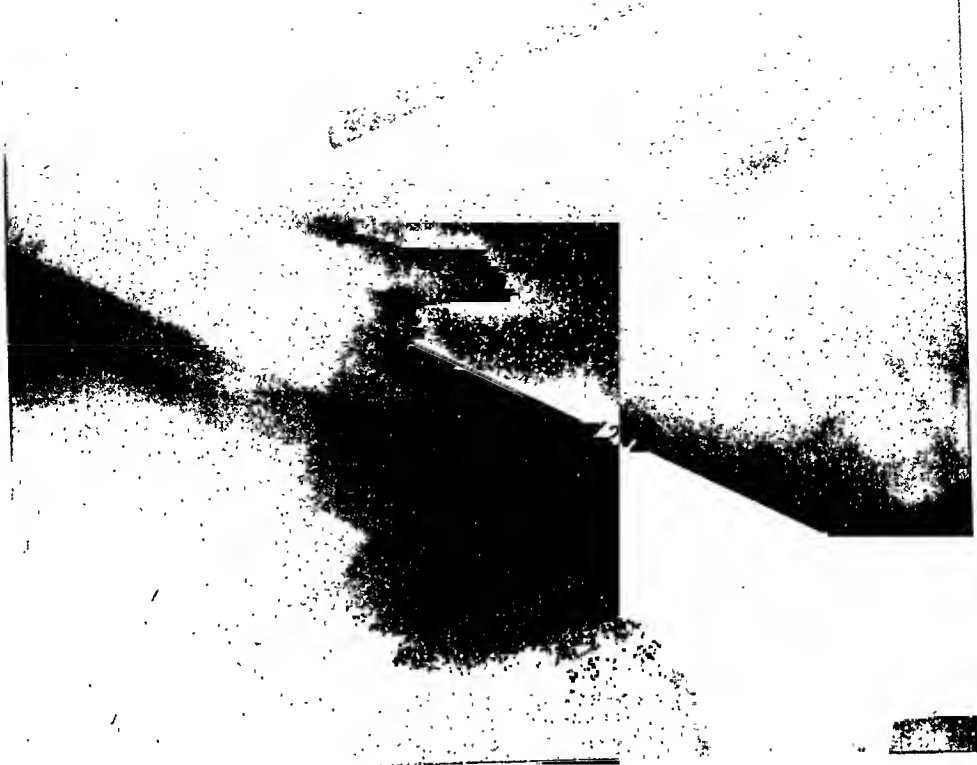
Fig. 8-A.

Fig. 8.—A pair of radiograms illustrating a transition type of pelvis with a promontory and a sacral prominence below it. Here the functioning conjugate must be plotted to this sacral prominence. Walcher's position *decreases* the length of the functioning (lower) conjugate by 0.2 cm. while not affecting the (upper) conjugate.

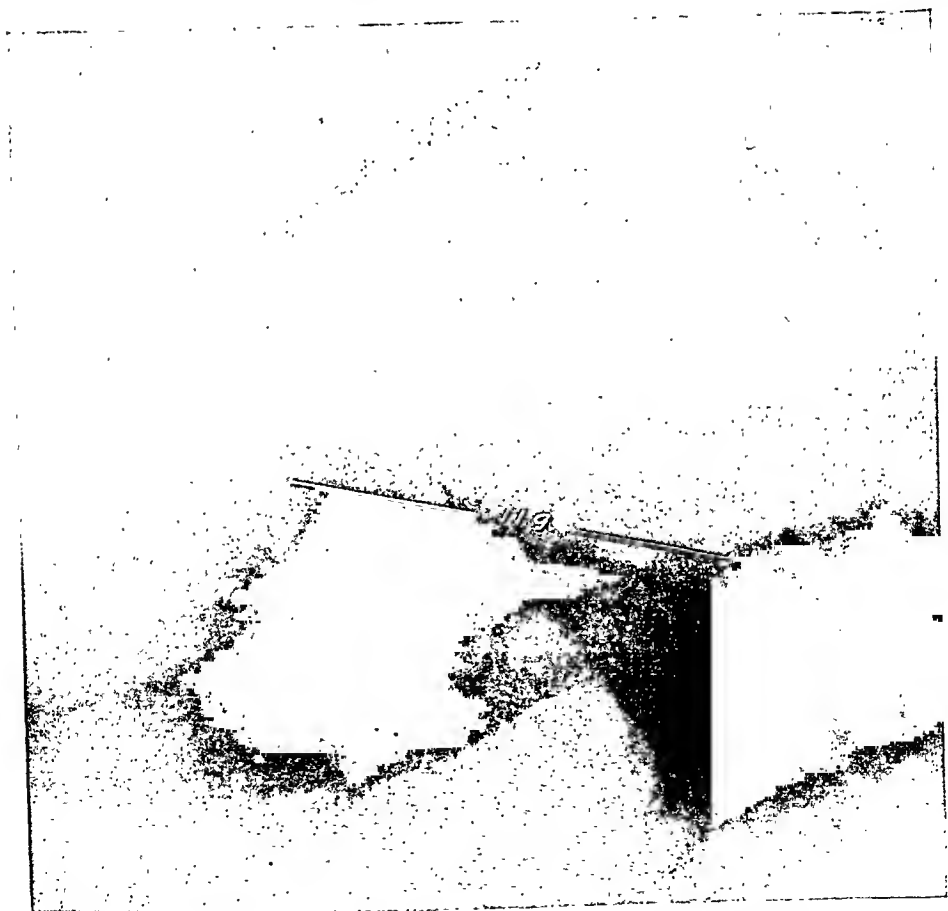
are equidistant from the film. The second condition demands that the base lines be exactly parallel. This, too, is easily secured by careful centration and by avoiding any such tilting of the ruler which would bring one end closer to the film than the other. By this method, the measurement of the obstetric conjugate is proved to be reliable within a range of approximately  $\pm 0.2$  cm.<sup>13, 18, 24</sup>

Representative illustrations from our study are inserted below to demonstrate the essential features of our investigation.

Fig. 6 is a lateral view of the pelvis measured by the metal rod method with the actual measurements and pertinent equation thereon.



A.



B.

Fig. 7.—Pair of radiograms taken in the slightly flexed (A) and Walcher (B) positions demonstrating that comparison and measurement can be accurately performed. The conjugate in the dorsal position equals 12.1 cm. and in Walcher position 11.9 cm. The result is a decrease of 0.2 cm.



located by anatomists at a point posterior to and below the promontory (*A*). Using *A* as the *center of rotation*, the theoretical position of the symphysis in Walcher's position (*W*), and in lithotomy position (*L*) was *geometrically determined*. These determined positions result in a shortening of the conjugate of 0.3 cm. in Walcher's position (*W*) but in a lengthening of 0.5 cm. in lithotomy position (*L*). Thus do we find the theoretical foundation of DeLee's clinical observation that in

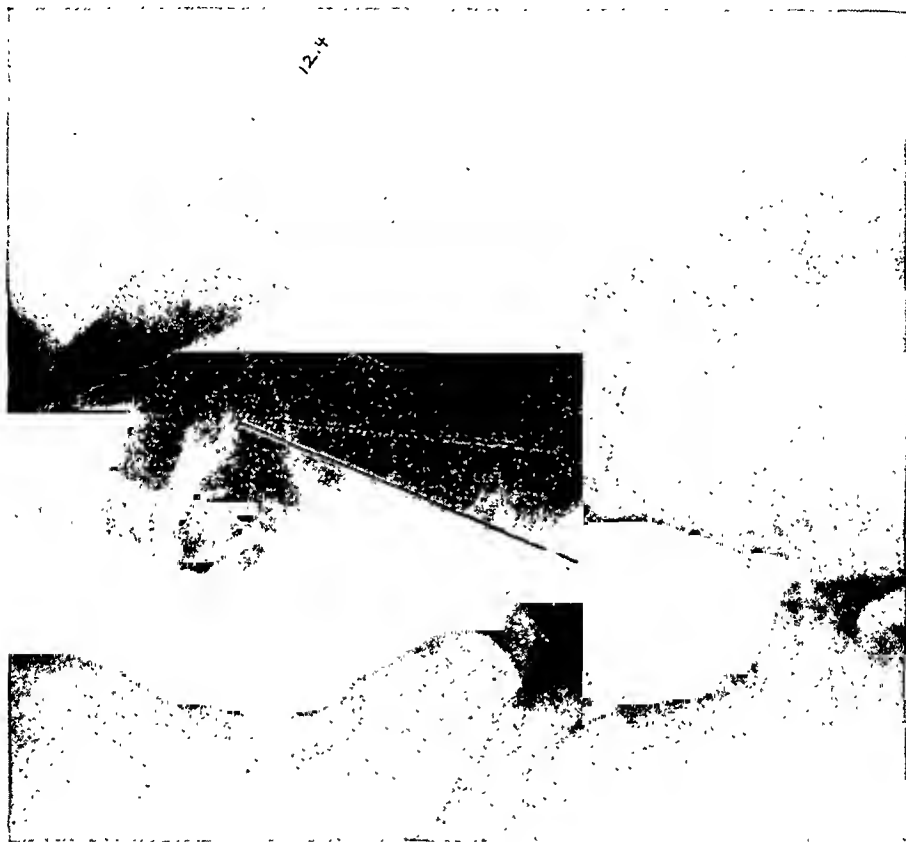


Fig. 9.

Figs. 9 and 10.—X-ray film and diagram of this film in which the functioning conjugate must be plotted to such an anterior sacral prominence (*P<sub>2</sub>*) as was shown in the previous illustration. Geometrically, the positions of the symphysis in the lithotomy (*L*) and Walcher (*W*) positions are determined. Again Walcher's position *shortens* the functioning conjugate (9.5 cm.) while the lithotomy position considerably *lengthens* it (10.3 cm.), thus contraindicating Walcher's position.

some cases he "curiously observed as good or better results with the exaggerated lithotomy position." The above described pelvis represents a group wherein Walcher's posture is contraindicated during the conduct of labor, while lithotomy position may have a beneficial effect.

Fig. 11 shows a similar geometrical determination for dorsal (*D*) and lithotomy (*L*) position in a *normal profile pelvis* with a good sacral excavation. Here lithotomy position brings about a definite shortening of the conjugate (0.7 cm.) compared with its original length in the comfortable dorsal position. This shortening of 0.7 cm. represents the increase in length of the obstetric conjugate which Walcher erroneously claimed for his posture. By comparing his posture to the lithotomy position instead of to the dorsal position, Walcher shortened the conjugate and then recovered this loss.

Fig. 7 is a comparative study of the pelvic inlet in the moderately flexed (*A*) and the Walcher (*B*) position, demonstrating a shortening of 0.2 cm. in the true obstetric conjugate in Walcher's position.

Fig. 8 is a comparative study of a transition type of pelvis in the dorsal (*A*) and the Walcher (*B*) positions. There is present an anterior sacral prominence at the junction of the first and second sacral segments. Here the functioning obstetric conjugate must be plotted from the symphysis to this anterior sacral prominence rather than to the anatomic promontory. Measurements of both conjugates are inserted for comparison and show that the functioning conjugate is 0.5 cm. and

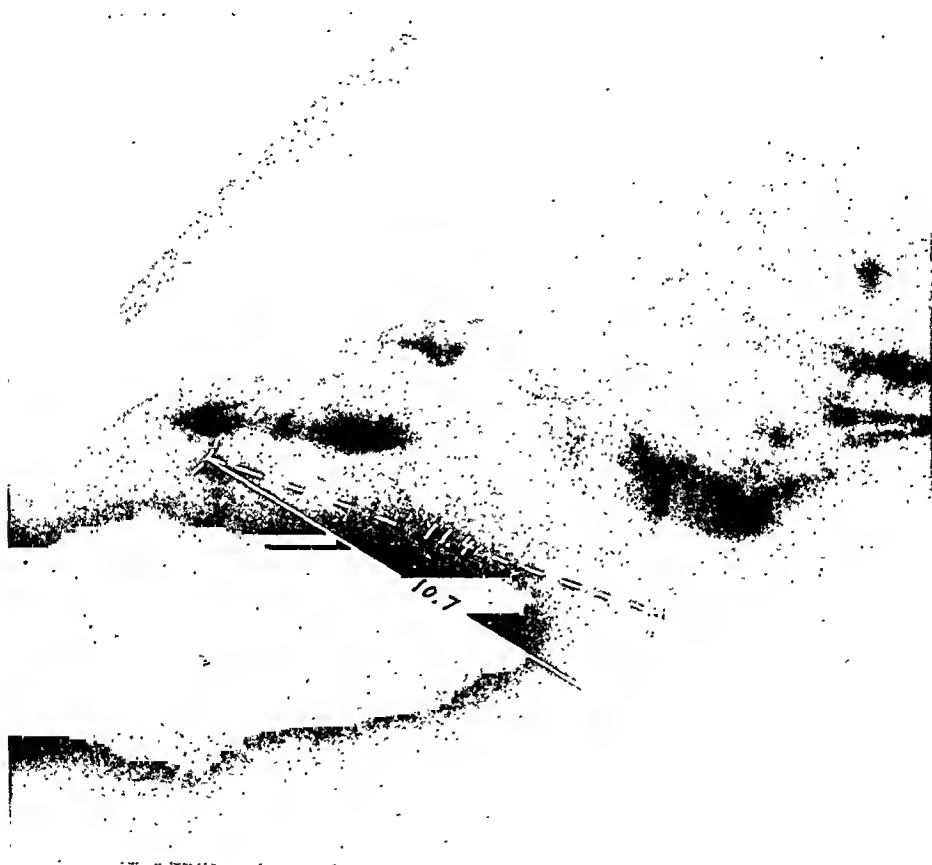


Fig. 8-B.

0.7 cm., respectively, shorter than the anatomic conjugate in both positions. Walcher's position (*B*) causes a shortening of 0.2 cm. in the functioning conjugate while the anatomical conjugate is unaffected.

Fig. 9 shows another transition type of pelvis with a marked anterior sacral prominence.

Fig. 10 is a superimposed tracing of this pelvis with several geometrically determined hypothetical positions of the symphysis inserted. *D* is the normal symphyseal position as traced directly from the x-ray film. Again, the functioning conjugate must be plotted to the anterior border of the sacrum ( $P_2$ ) while "routine" (thoughtless) plotting to the anatomical promontory ( $P_1$ ) would result in a measurement 1.1 cm. in excess of the correct length (9.8 cm. as against 10.9 cm.).

The transverse axis of rotation of the anterior pelvic ring, in the sacroiliac junctions, the key principle of Walcher's theory, has been

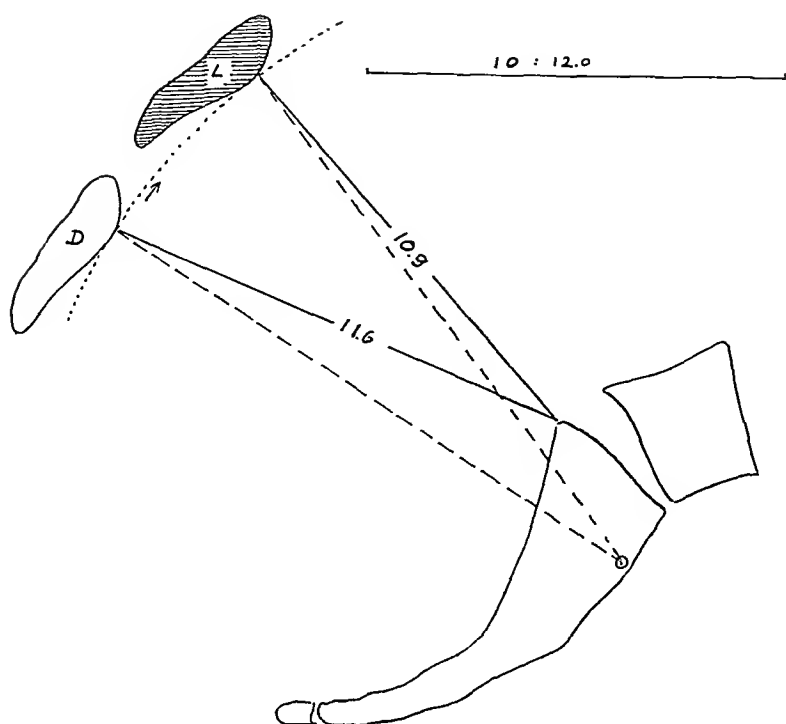


Fig. 11.—Diagram of a pelvis with a normal profile, demonstrating that the lithotomy position (*L*) decreases the length of the obstetric conjugate (10.9 cm.) as compared to its length of 11.6 cm. in comfortable dorsal position (*D*).

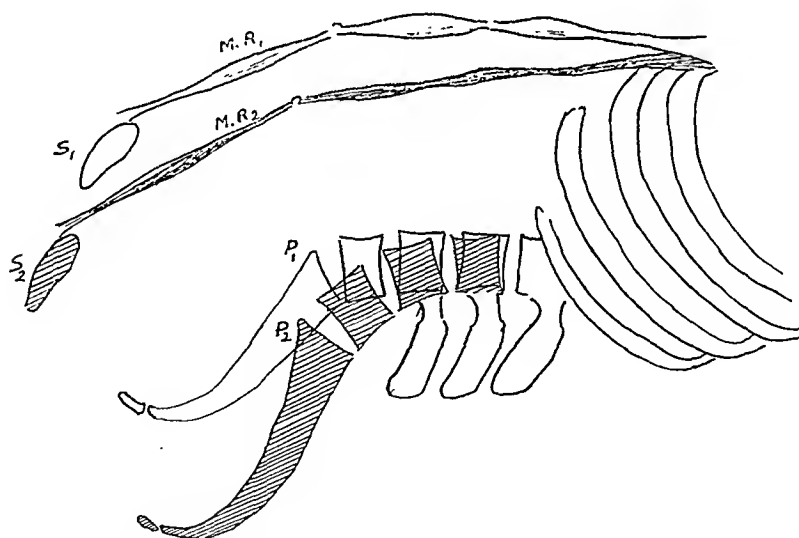


Fig. 12.—Demonstration of our theory concerning the efficiency of Walcher's position. Cross section through a pelvis, lumbar spine and abdominal rectus muscles in dorsal and in Walcher's positions (shaded). The distance from the origin to the insertion of the rectus muscles ( $M.R_1$  and  $M.R_2$ ) is materially increased in Walcher's posture and greatly increases the power of the auxiliary abdominal musculature (*Bauchpresse*). We also note the change in the angle of inclination of the pelvic inlet. Both factors may facilitate the entrance of the fetal head into the pelvis.

In our series twenty patients were studied, ten in labor and ten during gestation. Seven of each group were x-rayed in the comfortable dorsal position, and the remaining three in the moderately flexed position. In each patient comparative measurements were made with the Walcher position. Attempts to measure the conjugate in the exaggerated lithotomy position have, thus far, been unsuccessful. Tables I, II, and III illustrate the details.

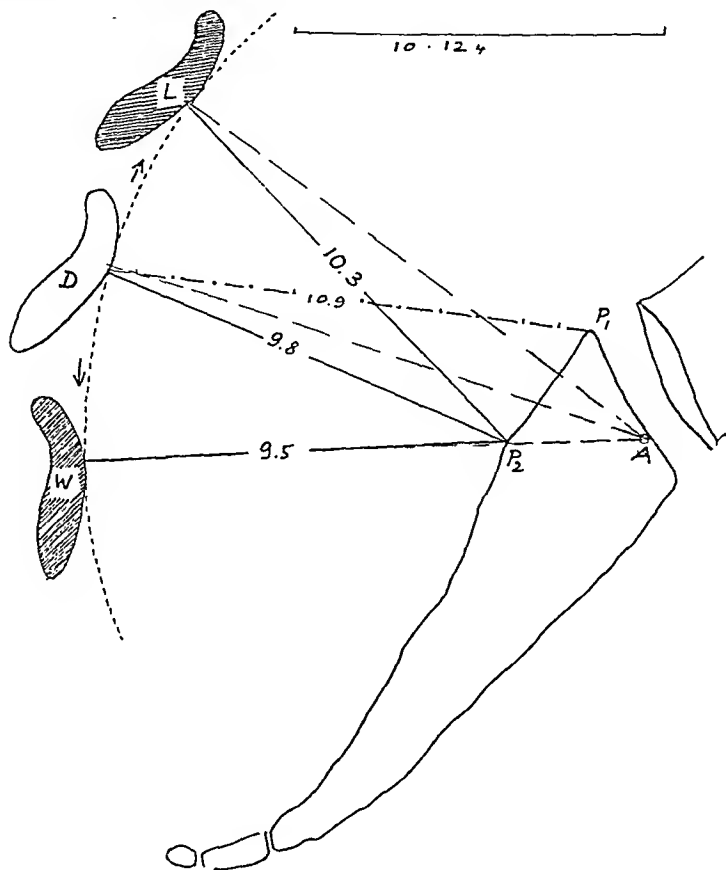


FIG. 10.

#### DISCUSSION

These results would indicate, that, in the average, the length of the obstetric conjugate, comparing the comfortable dorsal with Walcher's position, shows a negligible change of about 0.25 cm. Shortening occurs twice as frequently as lengthening. However, when comparing the moderately flexed position with Walcher's position an only apparent increase in the length of the obstetric conjugate averaging about 0.4 cm. is observed. This apparent lengthening actually is only the recovery of the original *shortening* of the obstetric conjugate which shortening was artificially produced through the change from the comfortable dorsal to the lithotomy position.

In none of our cases, comparing the various positions, did we even approach as great an increase in the obstetric conjugate "of from 0.8 to 1.3 cm." as claimed by Walcher.

Inasmuch as clinical observations of noted obstetricians for many years past have established the efficiency of the Walcher position, we

TABLE III.

NUMBER OF CASES	INCREASE	DECREASE	UNCHANGED
<i>Comparison of all cases of dorsal and Walcher's position</i>			
14	4, average + 0.35 cm.	8, average - 0.2 cm.	2
<i>Comparison of all cases of flexed and Walcher's position</i>			
6	5, average + 0.4 cm.	1, average - 0.2 cm.	0

must therefore search for the true causes of such beneficial effects, disregarding any lengthening of the conjugate. We offer the following as possible explanations. The angle of inclination of the pelvic inlet is considerably altered (Jarcho, Jacobs) in Walcher's position, through, we believe, increased lordosis of the lumbar spine, and thus may facilitate the entrance of the fetal head. Furthermore, there results a considerable increase in distance from the origin to the insertion of the rectus muscles (Fig. 12) in Walcher's posture.

According to an important law of muscular physiology,<sup>23</sup> the power of a muscle is greatly increased as its tension at rest increases and vice versa. Consequently the power of the auxiliary abdominal muscular apparatus (Bauchpresse) is greatly increased in Walcher's posture and may also act as a lever to guide the head into the inlet.

Further roentgenographic studies are indicated concerning the behavior of the lower lumbar spine and lumbosacral junction, and the behavior of the fetal head in Walcher's posture. All these studies may ultimately lead to the discovery of a procedure less distressing to the patient yet preserving the clinical advantages claimed for Walcher's position.

#### CONCLUSIONS

1. As compared to the comfortable dorsal position, Walcher's position does not *increase* the length of the obstetric conjugate, in a normal, profiled pelvis.

2. As compared to the comfortable dorsal position, the exaggerated lithotomy position *decreases* the length of the obstetric conjugate, in a normal profiled pelvis.

3. The *shortening* of the obstetric conjugate in the exaggerated lithotomy position led Walcher to the erroneous conclusion that the conjugate is *lengthened* in the position he advocated.

4. In difficult breech extraction, in a normal profiled sacrum, it is deemed advisable to change from lithotomy to Walcher position for delivery of the shoulders and aftercoming head, because the artificially *shortened* conjugate will thus recover its loss.

5. In flat sacrum pelvis with an anterior sacral prominence, Walcher's position is contraindicated, while lithotomy position will give additional space at the inlet.

6. The two factors of increased muscular tension and altered angle of inclination may explain the reputed clinical efficiency of Walcher's position.

TABLE I. STUDIES DURING PREGNANCY

CLINICAL DATA	OBSTETRIC CONJUGATE		SPECIAL FEATURES	DIFFERENCE CM.
	DORSAL	WALCHER		
<i>Comparison of comfortable dorsal with Walcher's position</i>				
1. L. C., para iii 32 weeks	11.0	11.0	Flat sacrum	±0
2. A. D., para i 30 weeks	12.0	12.2		+0.2
3. F. R., para i 32 weeks	13.7	13.6		-0.1
4. L. S., para ii 25 weeks	13.3	12.9		-0.4
5. S. C., para ii 30 weeks	11.9	12.3		+0.4
6. L. A., para iii 36 weeks	11.9	11.8		-0.1
7. A. S., para i 30 weeks	12.5	12.4		-0.1
7 cases		Increase 2 No change 1 Decrease 4	Average 2 Average 1 Average 4	+0.3 cm. 0 cm. -0.2 cm.
<i>Comparison of moderately flexed with Walcher's position</i>				
1. S. L., para ii 27 weeks	12.1	11.9		-0.2
2. J. S., para ii 25 weeks	11.9	12.1		+0.2
3. L. L., para i at term	11.5	12.0		+0.5
3 cases		Increase 2 Decrease 1	Average 2 Average 1	+0.35 cm. -0.2 cm.

TABLE II. STUDIES IN LABOR

CLINICAL DATA	OBSTETRIC CONJUGATE		SPECIAL FEATURES	DIFFERENCE CM.
	DORSAL	WALCHER		
<i>Comparison of comfortable dorsal with Walcher's position</i>				
1. C. Z., para i 2nd stage, +1, 8 cm.	10.7	10.7	Assimilation pelvis	0
2. A. R., para i 2nd stage, +1, 6 cm.	11.9	12.1		+0.2
3. M. S., para i 2nd stage, +2, 8 cm.	11.7	11.3		-0.4
4. I. P., para i 2nd stage, +2 complete	11.7	12.3		+0.6
5. M. D., para i 1st stage, 0, 6 cm.	13.4	13.3	Prominent first sacral disc	-0.1
6. S. G., para i 1st stage, 0, 3 cm.	{11.4 10.9	11.4 10.7		0 } -0.2 }
7. R. B., para i 1st stage, -1, 4 cm.	12.1	12.0		-0.1
7 cases		Increase 2 No change 1 Decrease 4	Average 2 Average 1 Average 4	+0.4 cm. 0 cm. -0.2 cm.
<i>Comparison of moderately flexed with Walcher's position</i>				
1. S. S., para i 1st stage, -2, 2 cm.	13.2	13.5	Marked flexion of thighs	+0.3
2. B. T., para i 2nd stage, +1, 8 cm.	10.2	10.4		+0.2
3. B. S., para i 2nd stage, +1, 6 cm.	11.0	11.8		+0.8
3 cases		Increase 3	Average 3	+0.13 cm.

# HEMORRHAGIC DIATHESIS OF THE NEWBORN

## EFFECT OF VITAMIN K PROPHYLAXIS AND THERAPY

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HEMORRHAGIC disease of the newborn has been recognized as a clinical entity for many years; for a complete discussion of the subject, the reader is referred to the excellent monograph of Salomonsen.<sup>1</sup> The prophylactic and curative effect of preparations having vitamin K activity has been demonstrated. A comprehensive survey by Brinkhous<sup>2</sup> contains most of the present knowledge concerning vitamin K.

The principal objective of our investigation was to evaluate the prophylactic effect of antenatal administration of menadione (2-methyl-1,4-naphthoquinone<sup>3</sup>) to mothers; a few observations on treatment have also been made. The responsibility for the study was divided; one of us (W. E. P.) supervised the therapy of the mothers; another (H. S. McK.) examined the eye grounds of the infants; and the third (L. G. P.) made serial determinations of microprothrombin time in the babies and instituted treatment when necessary. Measurements of prothrombin time were not made on the mothers, as no constant correlation has been found<sup>4-6</sup> between the levels in mothers and their infants. Determinations of coagulation time were made on a relatively small number of the babies simultaneously with the prothrombin times.

The expectant mothers were divided into three categories. One group received menadione before delivery for periods varying from three days to six weeks; a second group was treated during labor; a third was given no medicinal vitamin K. A preparation of 2-methyl-1,4-naphthoquinone in tablet form\* was used.

### TECHNIQUE OF DETERMINING PROTHROMBIN TIME

For the determination of prothrombin times a simple bedside method was used, based on a procedure suggested by Quick,<sup>7</sup> and incorporating features utilized by Ziffren and his associates<sup>8</sup> and by Kato.<sup>9</sup> Since the completion of this investigation the application of an almost identical method has been reported by Lawson.<sup>10</sup>

Thromboplastin is prepared from the fresh brain of a young rabbit by removing vessels and meninges, grinding in a mortar and extracting with cold acetone at least four times, then removing the excess acetone by filtration. The residue is dried in the incubator overnight at 37° C. The resulting powder will retain its potency for approximately a month if kept tightly stoppered in a refrigerator. In order to prepare the

\*Proklot, Eli Lilly and Co.

7. Theoretically, a device such as a low abdominal pressure-band and an elevation of the lumbar spine to a moderate lordosis may produce the advantages claimed by Walcher in a far less distressing manner to the patient.

We wish to express our gratitude to Dr. Aaron E. Kanter, chief of the first Gynecological Service of the Mount Sinai Hospital, for his generous aid and kind suggestions in the preparation of this study.

## REFERENCES

- (1) *Bell, J. W.*: AM. J. OBST. & GYNEC. 2: 616, 1921. (2) *Chamberlain, W. E.*: Am. J. Roentgenol. 24: 621, 1930. (3) *Christiani, J.*: Wien. klin. Rundschau. 27: 499, 465, 485, 1913. (4) *Coats, A. J.*: Northwest Med. 26: 542, 1927. (5) *Cutts, R. E.*: Ann. Gynaec. & Pediat. 13: 594, 1899-1900. (6) *DeLee, J. B.*: The Principles and Practice of Obstetrics, ed. 7, Philadelphia, 1938, W. B. Saunders Co., p. 809. (7) *Dice, W.*: Am. J. Obst. 63: 459, 1911. (8) *Dickinson, R. L.*: Am. J. Obst., N. Y. 39: 751, 1899. (9) *Duehrssen: Gesellschaft. f. Gynäk.* 5: 46, 1893. (10) *Fehling, II.*: Muenchen. med. Wehnschr 41: 861, 1894. (11) *Fothergill, W. E.*: Brit. M. J. 2: 1290, 1896. (12) *Goldthwaite, Joel E., and Osgood, R. B.*: Boston M. & S. J. 152: 593, 1905. (13) *Guthmann, H.*: Arch. f. Gynäk. 133: 415, 1928. (14) *Jacobs, J. B.*: AM. J. OBST. & GYNEC. 15: 689, 1928. (15) *Jarcho, Julius*: Surg., Gynec. & Obst. 49: 854, 1929. (16) *Kalt, A.*: Cor.-Bl. f. Schweiz. Aerzte. 24: 652, 1894. (17) *Klein, G.*: Ztschr. f. Geburtsh. u. Gynäk. 21: 74, 1891. (18) *Liepman, W., and Danielius, G.*: Geburtsh. u. Roentgenbild. p. 171, 1932. (19) *Litzenberg, J. C.*: J. A. M. A. 69: 1759, 1917. (20) *Lynch, F. W.*: Surg., Gynec. & Obst. 30: 575, 1920. (21) *Sellheim, H.*: Halban Seitz, Biologie u. Pathologie des Weibes, vii, 1, 102. (22) *Spencer, H.*: Lancet 1: 1568, 1912. (23) *Steindler, A.*: Mechanics of Normal and Pathological Locomotion in Man, Charles C Thomas, 1935, pp. 76, 129. (24) *Thoms, H.*: J. A. M. A. 85: 253, 1925. (25) *Idem*: Am. J. Surg. 47: 691, 1940. (26) *Idem*: AM. J. OBST. & GYNEC. 38: 634, 1939. (27) *Idem*: Am. J. Roentgenol. 44: 9, 1940. (28) *Titus, P.*: Management of Obstetrical Difficulties, ed. 1, St. Louis, 1937, The C. V. Mosby Co., p. 451. (29) *Wahl, F. A.*: Arch. f. Gynäk. 142: 668, 1930. (30) *Walcher, G.*: Zentralbl. f. Gynäk. 51: 892, 1889. (31) *Idem*: St. Louis Courier Med. 21: 341, 1899. (32) *Wehl, E. J.*: Arch. f. Gynäk., Berl. 45: 323, 1893-4. (33) *Williams, J. W.*: Obstetrics, ed. 5, New York, 1923, D. Appleton-Century Co., p. 865. (34) *Winter, G.*: Halban Seitz. Biologie u. Pathologie des Weibes, viii, 2, p. 231.

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Sadusk, Jr., Waters, and Wilson: The Treatment of Anuria Due to Sulfapyridine Calculi, J. A. M. A. 115: 1968, 1940.

The authors offer this report as a means of additional evidence that complete anuria due to sulfapyridine may be caused by ureteral obstruction and that this condition can be treated effectively by means of cystoscopy. The concretions may exist without blocking the ureters, and under these circumstances treatment of sulfapyridine hematuria by means of forced fluids alone seems ample, since data have been offered to suggest that the concretions may be redissolved or washed out. If complete anuria is present, cystoscopy and ureteral catheterization should be carried out, and the kidney pelvis should be thoroughly washed with warm water until urine drips from the catheter. This is followed by a retrograde pyelogram to outline the upper urinary tract. It is preferable to leave the catheters in for the next twelve hours and force fluids. Both acidity and alkalinity of the urine have been claimed as etiologic factors. Low urinary output has been advanced as an additional factor. The question of the sodium salt of sulfapyridine being more toxic than sulfapyridine itself as far as urinary symptoms are concerned is also discussed. Other pathologic changes in the upper urinary tract consist of tubular and capsular dilatation, marked congestion and vacuolization within the glomerular tufts, and an acute hemorrhagic pyeloureteritis extending into the adjacent renal medullary tissue.



The effect of administering menadione to the mother may be seen by referring to Figs. 2 and 3. Fig. 2 shows the microprothrombin curves of 54 infants of mothers treated during labor. Fig. 3 presents similar curves of 25 infants of mothers treated before labor. There is no de-

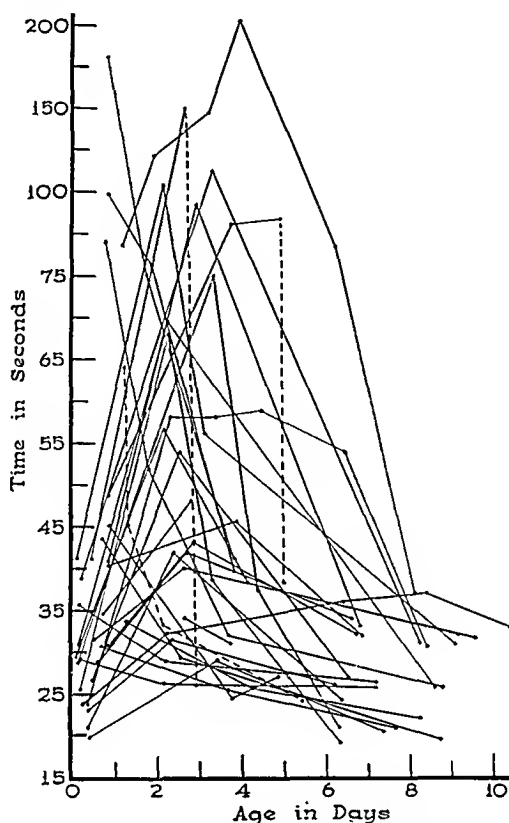


Fig. 1.—Microprothrombin times of 32 infants of untreated mothers. Broken lines represent the result of vitamin K therapy to the baby.

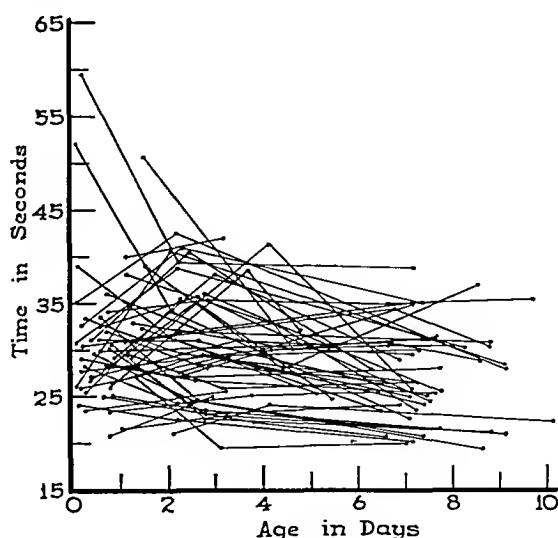


Fig. 2.—Microprothrombin times of 54 infants of mothers treated with vitamin K during labor.

suspension of thromboplastin for use in the test, 0.3 Gm. of the powder is thoroughly shaken with 5 e.e. of isotonic sodium chloride solution in a clean test tube, which is then placed in a water bath at 45° C. to 50° C. for from ten to fifteen minutes. The thromboplastin suspension is then ready for use; it may be employed for several days if kept in the refrigerator when not needed; its potency is checked daily by estimating the microprothrombin time of a healthy adult. Before use the suspension is shaken and allowed to settle; the turbid supernatant fluid is utilized. It should be allowed to come to room temperature before use.

The required apparatus includes several 0.1 c.e. pipettes, small glass rods, a stop watch, a porcelain spot plate, and a pointed knife blade. The test is made at the infant's bedside. The heel is cleaned with alcohol and an incision is made about 2 mm. long and approximately the same depth; the heel is then wiped vigorously with a dry sponge to stimulate the flow of blood. One-tenth cubic centimeter of blood is drawn up in a pipette; if that amount cannot be easily obtained as little as 0.05 c.e. can be used. The blood is immediately transferred to the spot plate, and an equal amount of thromboplastin suspension quickly added. Simultaneously the stop watch is started and the mixture is agitated with a small glass rod. Vigorous stirring is continued for five seconds, after which the rod is drawn slowly back and forth through the mixture to determine the end point, which is the time when the preparation gels. The watch is stopped at the instant clotting is perceived.

The time required for coagulation to occur is designated as the microprothrombin time. In over 90 per cent of the normal control determinations the microprothrombin time was between seventeen and twenty-six seconds. This represents a greater variation than that reported by Lawson,<sup>10</sup> due probably to less uniformity in our thromboplastin preparation. That this factor is the chief one is suggested by improved uniformity in a small number of determinations made more recently with a standardized preparation.\*

The performance of the test is simple; repeated determinations can easily be made on the same infant; this is not feasible with the usual methods requiring venous blood. The general plan was to perform the test on the first, third, and seventh days of life, but this schedule was varied in individual cases.

#### OBSERVATIONS OF PROTHROMBIN TIME IN INFANTS

Curves showing the microprothrombin times of 32 normal full-term infants whose mothers received no vitamin K are seen in Fig. 1. In general there is a tendency toward prolongation on the second and third days with a gradual return to normal after that time, but there are marked individual variations; several babies showed extreme prolongation on the first day. Two of these infants bled abnormally; a third had a cephalhematoma; the prothrombin times of all three responded promptly to vitamin K in oil,† given by mouth in two cases and in one case intramuscularly. In the two babies with external bleeding, the hemorrhage stopped within two hours after treatment; it was difficult to evaluate the effect on the cephalhematoma, although no further enlargement was noted.

\*Bacto-Thromboplastin (from rabbit brain), Difco Laboratories, Detroit, Michigan.

†Thyloquinone (2-methyl-1, 4-naphthoquinone) in oil, Squibb.

general their microprothrombin times are much more prolonged on the second and third days than is true in the bottle-fed babies (Fig. 5). The latter tend to approach normal values rapidly without undergoing the prolongation characteristic of the breast-fed infants. Fig. 6 shows the contrast in prothrombin levels which occurred in double ovum twins after the first day; the breast-fed infant developed hemorrhagic disease which responded to menadione (case 1), while the bottle-fed baby maintained a normal course.

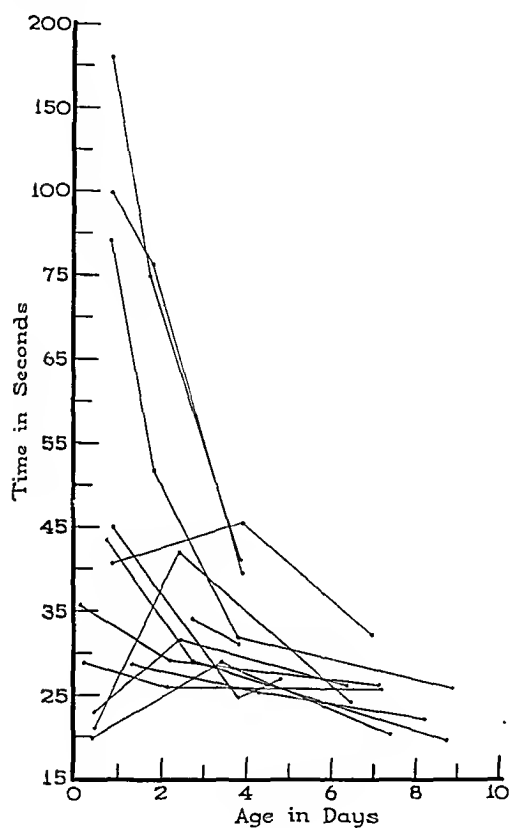


Fig. 5.

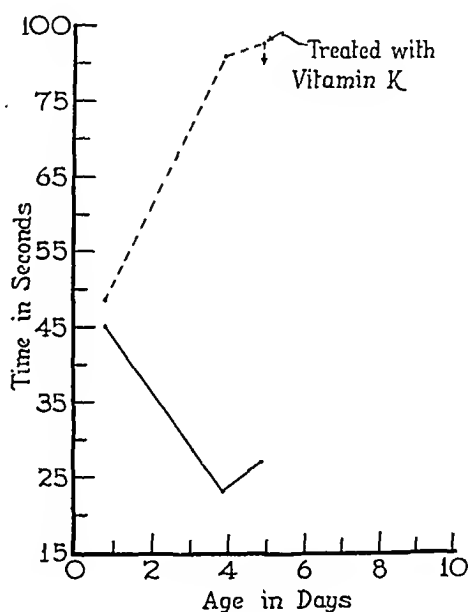


Fig. 6.

Fig. 5.—Microprothrombin times of 13 bottle-fed infants of untreated mothers.

Fig. 6.—Breast fed entirely -----, B. W., 3,470 Gm., male. Bottle fed entirely ———, B. W. 2,420 Gm., female. Microprothrombin times of binovular twins of an untreated mother. The larger infant was breast fed, the smaller bottle fed.

#### RETINAL HEMORRHAGES

Examination of the fundi was made in almost every infant; this was done during the first ten days, in the majority of cases during the first seventy-two hours. It is occasionally difficult to obtain a good view of the eye grounds during the first two or three days if the infant has chemical conjunctivitis. Ordinarily it may be done without too much difficulty if the pupils are dilated with homatropine, 0.5 per cent, and the baby appeased by means of a bottle containing sugar solution or formula.

Table I illustrates the striking decrease in the incidence of retinal hemorrhages in the infants of treated mothers as compared to the in-

monstrable difference between the two groups. Both fail to show the prolongation of prothrombin times ordinarily seen in the untreated cases.

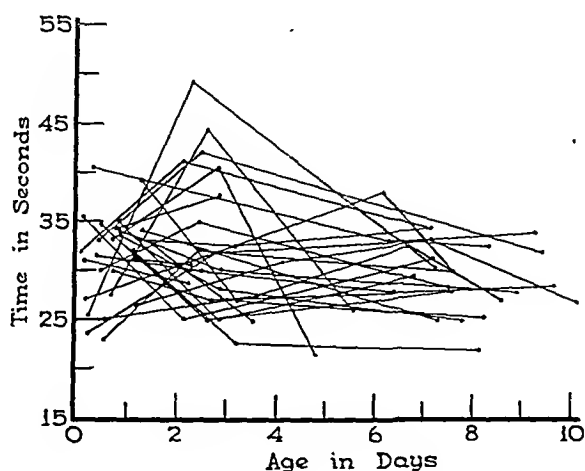


Fig. 3.—Microprothrombin times of 25 infants of mothers treated with vitamin K prior to labor.

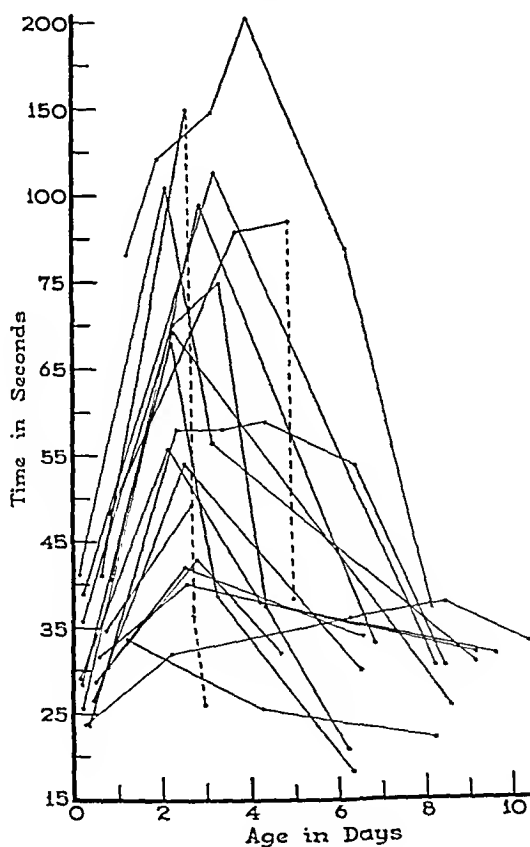


Fig. 4.—Microprothrombin times of 18 breast-fed infants of untreated mothers.

There was conspicuous difference between the breast-fed and the bottle-fed infants of untreated mothers with respect to the types of microprothrombin curves. Fig. 4 shows the breast-fed infants; in

the coagulation time was  $1\frac{3}{4}$  minutes. Two days later the microprothrombin time was approximately the same. The baby was discharged on the tenth day in good condition.

The course of the other twin was in marked contrast to that of the boy just described (Fig. 6). The girl weighed 2,420 Gm. at birth; on formula feedings she gained satisfactorily and was 150 Gm. over birth weight by the tenth day. The microprothrombin time was normal after the first day.

CASE 2.—F., white male, was born during February, 1941, the second child of a normal mother, following a labor of 2 hours and a spontaneous vertex delivery. No vitamin K prophylaxis was given. Birth weight was 3,430 Gm. Moderate icterus appeared on the first day and persisted. Physical examination was otherwise negative and hemoglobin level and red and white blood cell counts were normal. The baby did well generally until the ninth day, when there was a small amount of oozing from the umbilical cord, which was beginning to loosen. On the tenth day profuse oozing from the umbilicus began suddenly, enough to soak through several abdominal binders and a number of gauze dressings before it was stopped. Microprothrombin time a few minutes after the onset of the bleeding had no end-point, and the coagulation time was longer than 15 minutes. Thyloquinone in oil, 2 mg., was given intramuscularly. Fifty minutes later there was still no end-point of the microprothrombin time, but the coagulation time was  $5\frac{1}{2}$  minutes; the bleeding had not diminished. A dressing moistened with epinephrine solution was applied with a tight binder, without demonstrable effect on the bleeding. More vitamin K (4 mg. of thyloquinone in oil) was given intramuscularly 25 minutes later,  $1\frac{1}{4}$  hours after the first dose. Ten minutes later the coagulation time was  $4\frac{3}{4}$  minutes, and bleeding time was  $1\frac{3}{4}$  minutes. The red blood cell count and hemoglobin level were essentially as on the first day; there were 2 nucleated erythrocytes per 100 leucocytes. Microprothrombin time  $2\frac{1}{2}$  hours after the first injection of vitamin K was 106 seconds, with a control of 23 seconds. By that time the oozing had become slight, and had been so for about one-half hour previously. The microprothrombin time 4 hours and 5 minutes after treatment was begun was 58 seconds; coagulation time was  $2\frac{1}{2}$  minutes. Bleeding had practically stopped. Two hours and 50 minutes later the microprothrombin time was 35 seconds; coagulation time was 2 minutes. No bleeding whatever was occurring at that time. The following day, 22 hours after institution of therapy, the microprothrombin time was 29 seconds, control 24 seconds; coagulation time was 2 minutes. The values remained within normal limits after that time.

CASE 3.—M., white male, was born during December, 1940, the seventh child of a normal mother who received no medicinal vitamin K. Labor lasted  $1\frac{1}{2}$  hours; delivery was spontaneous. Birth weight was 3,930 Gm. The microprothrombin time on the first day was 41 seconds, control 16 seconds; the coagulation time was 3 minutes. The baby was breast fed throughout, and took feedings well; at the time of discharge on the ninth day he was 130 Gm. under birth weight. On the second day of life the eye grounds showed no retinal hemorrhages. The following day the microprothrombin time was 150 seconds, with a control value of 22 seconds; the coagulation time was  $5\frac{1}{2}$  minutes. Vitamin K (2-methyl-1, 4-naphthoquinone) in oil, 2 mg., was administered intramuscularly into the buttock. An hour and thirty-five minutes later the microprothrombin time was 52 seconds, and the coagulation time was 4 minutes. A heel prick made almost 3 hours before was still oozing. Two hours and five minutes after therapy the microprothrombin time was 36 seconds; the coagulation time was  $2\frac{3}{4}$  minutes; oozing from the heel had stopped. Nine hours and twenty minutes after treatment the microprothrombin time was 26 seconds. The following day, a little less than 24 hours following the intramuscular vitamin K, the microprothrombin time was 27 seconds, with a control of 22 seconds. The course thereafter was uneventful.

#### DISCUSSION

Our results confirm the findings of others that the administration of vitamin K to expectant mothers either during the latter part of pregnancy or during labor results in approximately normal prothrombin

TABLE I. INCIDENCE OF RETINAL HEMORRHAGES IN INFANTS OF MOTHERS (A) WHO RECEIVED NO VITAMIN K, (B) WHO RECEIVED VITAMIN K DURING LABOR, (C) WHO RECEIVED VITAMIN K PRIOR TO LABOR

TOTAL CASES	INCIDENCE OF HEMORRHAGES		SIZE OF HEMORRHAGES	
	NO. OF CASES	PER CENT	SMALL	LARGER
(A) 25 untreated cases	11	44	7	4
(B) 53 cases treated during labor	10	19	4	6
(C) 23 cases treated prior to labor	3	13	3	0

idence among those who were untreated. There were retinal hemorrhages in 44 per cent of the untreated cases; some of the hemorrhages were fairly large; their incidence corresponds closely with that found in a previous study by McKeown<sup>11</sup> of 498 newborn infants. In the cases in which menadione was not given until after the onset of labor, retinal hemorrhages were present in 19 per cent; in over half of the cases the hemorrhages were moderately large. In the cases in which the mothers received menadione prior to labor, there were retinal hemorrhages in only 13 per cent; none of these hemorrhages were large. Statistical examination of these data by the method of chi-square demonstrates a highly significant difference between the infants of treated and those of untreated mothers; between the two treated groups there is no significant difference. However, the size as well as the number of hemorrhages provides some evidence that administration of menadione prior to the onset of labor may afford more effective prophylaxis. Maumenee and his associates<sup>12</sup> recently reported definite reduction in the incidence of retinal hemorrhages as a result of antenatal vitamin K therapy; this effect was significantly greater in the group treated before labor than in those treated during labor alone.

#### CASES OF HEMORRHAGIC DISEASE TREATED WITH VITAMIN K

CASE 1.—Y., colored male, one of double ovum twins, was born in January, 1941, following a labor of 15 hours and a spontaneous vertex delivery. Birth weight was 3,470 Gm. No vitamin K was administered to the mother; this was her second pregnancy. The infant was breast fed throughout the hospital stay, receiving, in addition, 5 per cent sucrose water during the first 3 days. Feedings were taken well; the weight dropped to a low figure of 3,120 Gm. on the fifth day; it was 3,270 Gm. on the tenth day. The microprothrombin time was 48.5 seconds on the first day, compared to a normal control of 25 seconds. Examination of the eye grounds on that day showed large and small flame-shaped hemorrhages above and below the optic discs. On the fourth day the microprothrombin time was 89 seconds, as compared with a control of 22 seconds. The next day the microprothrombin time was 93 seconds, with a control value of 18 seconds. The coagulation time was 4 minutes. It was discovered at that time that the heel prick from the previous day was still oozing, and vitamin K therapy was therefore thought to be indicated. Thyloquinone (2-methyl-1, 4-naphthoquinone) in oil, 2 mg., was given by mouth. One and one-half hours later the oozing had stopped; the microprothrombin time was 38 seconds, control 18 seconds. One and three-fourths hours after that the microprothrombin time was 43 seconds; the coagulation time was 2¼ minutes. An hour and one-half later the microprothrombin time was 37 seconds; the coagulation time had remained the same. The following morning, 23 hours after administration of vitamin K, the microprothrombin time was 19 seconds, with a control of 16 seconds;

hemorrhagic diathesis of the newborn. The danger zone appears to be between 70 and 100 seconds, but the variability of the bleeding level is demonstrated by one case in which a micropothrombin time of more than 200 seconds was unaccompanied by pathologic bleeding. In the three cases of hemorrhagic disease the estimations of coagulation time were made by the capillary tube method. The correlation with the prothrombin times is fairly good. We have not obtained a coagulation time of more than 2½ minutes in the presence of a normal micropothrombin time.

The reduction in the incidence of retinal hemorrhages in infants of mothers receiving vitamin K is significant because of the possible relationship between retinal and intracranial bleeding. It is recognized that difficult labors and instrumental deliveries contribute to the incidence of intracranial hemorrhage;<sup>1</sup> McKeown<sup>11</sup> has shown that the same factors affect the incidence of retinal hemorrhage. The frequency of difficult labors in our series appears to be evenly distributed throughout the treated and untreated cases. Hellman and his coworkers<sup>16</sup> report a substantial reduction in intracranial hemorrhage and mortality rate in infants whose mothers were given vitamin K during labor. In our cases there were no symptoms of intracranial hemorrhage and no deaths. The extent of the protection afforded can be accurately evaluated only by observation of a larger number of cases. It would not be surprising if the incidence of hemorrhage were lower when vitamin K therapy is instituted prior to labor than when it is given during labor alone, because in some of the latter cases considerable pressure may be exerted on the infant's head before administration of vitamin K.

#### SUMMARY

A simple test requiring only a small amount of capillary blood was utilized in making multiple determinations of prothrombin values in newborn infants. The test as described is accurate enough for practical purposes.

Treatment of expectant mothers with menadione (2-methyl-1, 4-naphthoquinone) during the last days of pregnancy or during labor virtually eliminated the hypoprothrombinemia and tendency toward pathologic bleeding as a result of hemorrhagic disease which otherwise may occur during the neonatal period.

The incidence of retinal hemorrhages in the newborn was markedly reduced in infants of mothers treated with menadione during labor or prior to labor. Our results suggest that the reduction is greatest in the cases in which treatment is instituted before the onset of labor. These findings are of particular interest in their possible relationship to intracranial hemorrhage.

The introduction of formula feedings during the first few days of life counteracted hypoprothrombinemia. The mechanism of this action is still not known.

Three infants with hemorrhagic disease of the newborn were rapidly cured by administration of vitamin K. In two cases this was administered intramuscularly, and in one case by mouth.

values in their infants and virtually eliminates the prolongation in prothrombin time which usually occurs in untreated cases between the second and fourth days of life. Menadione (2-methyl-1, 4-naphthoquinone) was used in treatment; it is one of the most potent preparations having vitamin K activity. This was given during the latter part of pregnancy in doses of 2 mg. three times a day in tablet form; it is likely that a dosage of 1 or 2 mg. daily would have accomplished the same result. Hellman and his associates<sup>6</sup> report better utilization of vitamin K in an oily medium than in pills made up with lactose. We did not try different amounts or different forms of the drug.

The dosage used during labor was 20 mg. in most cases; in a few instances in which 10 mg. were given, there was an equal prophylactic effect; again it is quite possible that smaller doses would have been equally effective. There was no direct correlation between the prothrombin times of the infant and the time interval between treatment and delivery except in one case in which less than an hour elapsed; in that case the microprothrombin times followed a curve typical of the untreated cases.

An incidental finding of some interest is that formula feedings during the first few days of life counteract the hypoprothrombinemia which occurs ordinarily in untreated cases if the baby is fed on the breast alone. In cases in which the initial prothrombin time was abnormally long, the introduction of formula feedings quickly brought the prothrombin time to a value close to normal. These findings agree with those of Salomonsen and Nygaard,<sup>13</sup> who attribute the difference to a more rapid development of intestinal flora in infants given supplemental feedings shortly after birth. They quote Almquist and his coworkers,<sup>14</sup> who found that some species of bacteria form a vitamin K active substance as a metabolic product. That this may not be the entire answer is suggested by a preliminary experiment in one of our infants who was given sulfanilylguanidine in full doses beginning twelve hours after birth; in spite of the fact that one might expect this drug to keep bacterial growth below usual levels in the intestinal tract,<sup>15</sup> the prothrombin time rapidly approached normal on formula feedings. It seems probable that the relative starvation during the first three days in breast-fed infants is the important factor in the failure to form prothrombin, but at present we are unable to go further than that. The vitamin K content of milk itself is said to be low.

The prompt curative action of menadione in oil in hemorrhagic disease of the newborn is shown in three such cases reported in detail. This acted with equal rapidity whether given by mouth or intramuscularly; the dosage was 2 mg. to 6 mg.; within two hours bleeding stopped entirely or almost completely in each instance. There was apparently no need to repeat the initial dose, although in one case associated with severe bleeding two injections were given about an hour apart. It is our feeling that the intramuscular route is the preferable one in severe cases, because the possibility of loss by vomiting is eliminated.

The microprothrombin time as measured in this study gives information which is accurate and easily obtained concerning the danger of



## THERAPY

As soon as the preliminary investigations had been completed, the patients were placed on estrogen therapy. The estrogens used were estradiol benzoate\* (4,000 to 10,000 R.U., 2 or 3 times weekly) and estradiol dipropionate† (1 or 2 mg., 3 times weekly, or 5 mg., once or twice weekly) in solution in sesame oil, administered intramuscularly.

## RESULTS

Some symptomatic improvement was noted in 7 cases as early as one week after the beginning of treatment, coincident with the appearance of estrogenic effect in the vaginal mucosa (Figs. 1, 2, 3, 4, and 5). At the end of two weeks, there was definite relief of symptoms in 12 of the 16 cases. With the exception of 3 cases (one of which was only moderately improved and 2, unimproved), the symptoms were completely controlled at the end of the fourth week of treatment.

Following the discontinuation of treatment, the patients remained symptom free for periods varying from six weeks to four months. Thereafter, symptoms returned with progressive severity. It was noted that recurrence of symptoms was accompanied by evidence of estrogen deficiency in the vaginal smears. These patients were subsequently given additional courses of estrogen therapy which resulted in disappearance of the symptoms. In several patients, the same cycle (recurrence of symptoms upon withdrawal of estrogens, followed by relief of symptoms after reinstitution of estrogen therapy) was repeated several times during the course of three years. The case history of one patient who has been under observation by one of us (U. J. S.) for 5 years, during which time she experienced 4 recurrences of symptoms, each time associated with characteristic estrogen deficiency smears, is given in detail. At each recurrence, symptoms responded promptly to estrogen therapy.

Case G. D., aged 56 years, was a gravida v, para iii, youngest child aged 27. Menstrual history, 14 by 28 by 5; menopause occurred at 51 years of age. The patient was first seen on Oct. 12, 1935, complaining of urinary incontinence which began shortly after the menopause and had grown steadily worse during the following two years. In addition, she complained of urinary frequency, dysuria, and vaginal irritation. General physical examination revealed nothing relevant. Pelvic examination revealed the orifice of the urethra to be markedly reddened and the surrounding mucosa to be spotted with minute, reddish erosions. The vaginal mucosa exhibited a characteristic picture of senile vaginitis. On straining, a small cystocele and urethrocele were evident. The uterus was atrophic, pelvic examination being otherwise negative. The vaginal smear and biopsy revealed an advanced degree of estrogen deficiency (Figs. 1 and 2). Cystoscopic and urinary examination were essentially negative. A diagnosis of senile vaginitis, urethrocele, and cystocele was made. The urinary incontinence was attributed to the urethrocele and cystocele. It was planned to do a urethroplasty for the cure of the incontinence; but, because of the senile vaginitis, it was felt advisable to treat this condition prior to operation. Accordingly, the patient was given 4,000 R.U. of estradiol benzoate, intramuscularly, 3 times weekly. At the end of one week, after a total of 12,000 R.U., the patient reported slight improvement and the vaginal smear revealed a definite, though incomplete, estrogen effect (Fig. 3).

\*For the estradiol benzoate (progynon-B) and the estradiol suppositories used in this investigation, we are indebted to Drs. Erwin Schwenk and Max Gilbert, of the Schering Corporation, Bloomfield, N. J.

†For the estradiol dipropionate (di-ovoclyn) used in this investigation, we are indebted to Mr. Robert C. Mautner, of Ciba Pharmaceutical Products, Summit, N. J.

## REFERENCES

- (1) *Salomonsen, L.*: Acta paediat. 27: Suppl. I, 1939. (2) *Brinkhous, K. M.*: Medicine 19: 329, 1940. (3) Council on Pharmacy and Chemistry: J. A. M. A. 116: 1054, 1941. (4) *Hellman, L. M., and Shettles, L. B.*: Bull. Johns Hopkins Hosp. 65: 138, 1939. (5) *Shettles, L. B., Delfs, E., and Hellman, L. M.*: Ibid. 65: 419, 1939. (6) *Hellman, L. M., Moore, W. T., and Shettles, L. B.*: Ibid. 66: 379, 1940. (7) *Quick, A. J.*: Proc. Soc. Exper. Biol. & Med. 42: 788, 1939. (8) *Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P.*: Ibid. 40: 595, 1939. (9) *Kato, K.*: Am. J. Clin. Path. 10: 147, 1940. (10) *Lawson, R. B.*: J. Pediat. 18: 224, 1941. (11) *McKeown, H. S.*: Tr. Am. Ophth. Soc. 38: 510, 1940. (12) *Maumenee, A. E., Hellman, L. M., and Shettles, L. B.*: Bull. Johns Hopkins Hosp. 68: 158, 1941. (13) *Salomonsen, L., and Nygaard, K. K.*: Acta paediat. 27: 209, 1939. (14) *Almquist, H. J., Pentler, C. F., and Mecchi, E.*: Proc. Soc. Exper. Biol. & Med. 38: 336, 1938. (15) *Marshall, E. K., Jr., Bratton, A. C., White, H. J., and Litchfield, J. T., Jr.*: Bull. Johns Hopkins Hosp. 67: 163, 1940. (16) *Hellman, L. M., Shettles, L. B., and Eastman, N. J.*: AM. J. OBST. & GYN. 40: 844, 1940.

## THE USE OF ESTROGENS IN THE TREATMENT OF DYSURIA AND INCONTINENCE IN POSTMENOPAUSAL WOMEN

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THE study reported here stems from the observation that a number of women with disorders of micturition, consisting of urinary frequency, urgency, and incontinence, experienced relief of these symptoms while being treated with estrogens for the usual menopausal complaints. In order to determine the relationship of the estrogen therapy to the amelioration of the urinary symptoms, a group of postmenopausal patients with urgency, dysuria, and stress incontinence were selected for study and treatment.

### METHODS AND MATERIALS

All patients were submitted to the routine gynecologic examination, urinalysis and observation cystoscopy. In order to determine, objectively, whether these women were suffering from estrogen deficiency, and also to evaluate the efficacy of the administered hormone, vaginal smear studies were performed during the period of preliminary observation and after the institution of estrogen therapy. The aqueous fuchsin technique for staining the vaginal smears<sup>1, 2</sup> was employed. (In 3 patients, the vaginal smear studies were supplemented with vaginal biopsies.)

A series of 16 cases was investigated. Six patients complained of urinary frequency, burning sensation on urination, and urgency; 10 complained also of incontinence on coughing, sneezing, or straining. The ages ranged from 57 to 72 years. Of the 16 patients, 10 were multiparas (para ii to xii); 2, primiparas; 1, nullipara; and 3, virgins. Four of the patients had moderate cystoceles and 2 urethroceles; 6 had clinical evidence of senile vaginitis. In the others, except for the presence of genital atrophy, consistent with the ages of the patients, there was no palpable pelvic organic disease. Cystoscopic examination revealed, in the majority, slight congestion of the trigone; in 2 there was also slight edema of the bladder sphincter. Repeated urinalysis in all of these patients failed to reveal a cause for the symptoms. The preliminary vaginal smears in all revealed cytologic evidence of marked estrogen deficiency.

weeks, for the following six weeks. She remained symptom-free for six weeks thereafter, without further treatment.

On April 22, 1936, the patient reported that the dysuria, urinary frequency, and incontinence had recurred several weeks before. Examination revealed a slight erosion of the urethral meatus and a moderate degree of senile vaginitis. The vaginal smear revealed a slight degree of estrogen deficiency. The patient

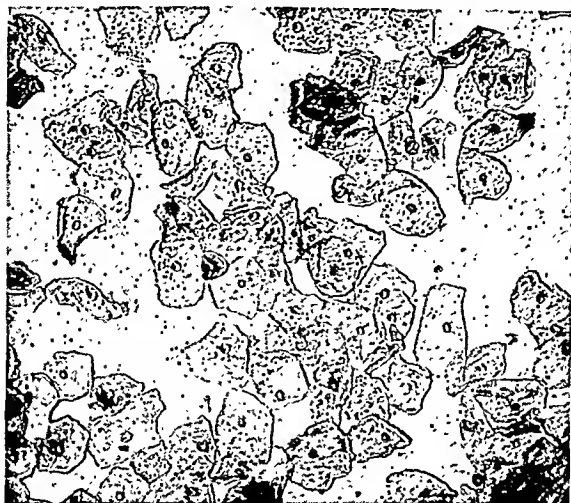


Fig. 4.—Case G. D. Vaginal smear taken three weeks after beginning of treatment, following total of 36,000 R.U. of estradiol benzoate. Incontinence and dysuria completely relieved. Note absence of leucocytes and "atrophy" cells and their replacement by large, squamous epithelial cells with small nuclei, indicating full estrogenic effect. ( $\times 200$ .)



Fig. 5.—Posttreatment vaginal biopsy taken at same time as smear in Fig. 4. Compare with Fig. 2. Note increased thickness of epithelial layer; vacuolization, marked proliferation of basal layer, absence of leucocytic infiltration. This histologic picture is indicative of a full estrogenic effect and is comparable to the vaginal mucosa in cyclical women with normally functioning ovaries. ( $\times 100$ .)

was then given 10,000 R.U. of estradiol benzoate and the same dose was repeated twice weekly. At the end of two weeks the symptoms were again completely relieved and the vaginal smear showed complete estrogenic effect. At this point, the patient developed uterine bleeding which continued for five days. She was, thereafter, given 10,000 R.U. every two weeks, for the following four months. The patient then remained symptom-free for four months without additional therapy, after which symptoms again recurred. Examination of the vaginal

Two weeks later, after a total of 36,000 R.U., the urinary symptoms, including the incontinence, were completely relieved. With a full bladder, and in the lithotomy position, the patient was not incontinent on coughing or straining. The eroded areas surrounding the urinary meatus were completely epithelized, the



Fig. 1.



Fig. 2.

Fig. 1.—Case G. D., aged 56 years, gravida v, para iii, had a natural menopause, 5 years previously. Complaints: dysuria and incontinence. Pretreatment vaginal smear (Oct 12, 1935) revealed "atrophy" cells, leucocytes, and erythrocytes, characteristic of advanced degree of estrogen deficiency and senile vaginitis. ( $\times 200$ .)

Fig. 2.—Pre-treatment vaginal biopsy taken at same time as smear in Fig. 1. Note atrophied epithelial layer, absence of cornification, intraepithelial and subepithelial leucocytic infiltration, characteristic of advanced degree of estrogen deficiency and senile vaginitis. ( $\times 100$ .)

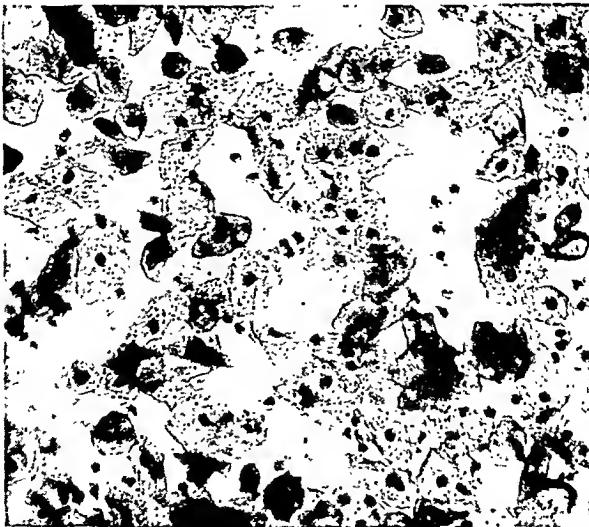


Fig. 3.—Case G. D. Vaginal smear (taken one week later) following the administration of 12,000 R.U. of estradiol benzoate. Slight symptomatic improvement. Note decreased number of leucocytes and "atrophy" cells; advent of large, squamous epithelial cells, indicating estrogenic effect (incomplete). ( $\times 200$ .)

vaginitis had completely disappeared, and the vaginal mucosa had a healthy, pinkish color. The vaginal smear and biopsy, at this time, revealed a full estrogenic effect (Figs. 4 and 5). The patient was then given 4,000 R.U., every two

vagina. Furthermore, both the histologic and physiologic integrity of the vagina are dependent upon an adequate supply of estrogens. Prolonged estrogen deprivation leads to a marked decrease in blood supply to the vagina and to atrophy of the muscularis as well as of the mucosa of the vagina. It seems logical to expect that these striking involutional changes would also affect the bladder sphincter, either directly, by impairing the intrinsic tone of its muscle fibers, or indirectly, because of the atrophy and atony of the muscularis of the vagina.

The relationship of the dysuria and urinary frequency to the estrogen deficiency still remains to be explained. The "trigonitis" which one finds so frequently in these patients, we believe, is an incidental finding, since similar degrees of congestion of the trigone are found without symptoms. We have been impressed with the fact that all of the patients with these symptoms had, in addition to advanced degrees of vaginal atrophy or senile vaginitis, a similar atrophic process involving the orifice of the urethra and the surrounding mucous membrane. The mucosa in these regions exhibited pin-point hemorrhagic and eroded areas. Urine coming in contact with the eroded areas causes pain, burning, and urinary frequency. Following treatment with estrogens, the pin-point erosions disappear and the meatus and periurethral mucosa, like the vaginal mucosa, become completely epithelized, assuming a smooth, uniformly pink appearance, coincident with relief of symptoms.

The 3 patients who did not respond satisfactorily to the estrogen treatment have remained unsolved problems. In 2 of these, the presence of an anatomic defect (cystocele) may account for the persistence of the symptoms, although other patients with lesions of apparently similar degree were benefited very strikingly by estrogens. Surgical repair was not feasible in these cases because of cardiovascular disease. The third patient was a virgin. Apparently incontinence may be attributable to still other factors aside from anatomic defects in the sphincter mechanism or estrogen deficiency. The possibility of psychogenic factors has been considered, and these patients are being studied from this angle.

The question arises as to why do not all elderly women develop urinary symptoms. The same question may be raised with regard to senile vaginitis. The answer appears to lie in the fact that not all postclimacteric women suffer from an estrogen deficiency. There is evidence which indicates that some women apparently produce estrogens for many years after the menopause or even after bilateral ovariectomy. Thus, some women exhibit morphologic evidence in the vaginal mucosa of estrogenic stimulation many years after the menopause<sup>1, 2</sup> and excrete estrogens even after bilateral ovariectomy.<sup>3, 4</sup> It is conceivable that the endogenous estrogens, which experimental evidence indicates are probably formed in the adrenal cortex,<sup>5</sup> may prevent the estrogen deficiency and its concomitant symptoms, for many years after the menopause.

On the basis of the observations reported here, we would suggest that elderly women with urinary incontinence be examined for estrogen deficiency before resorting to surgical measures, and, if signs of

smear again revealed evidence of estrogen deficiency. During the following three years, the patient experienced 2 additional recurrences associated with vaginal smear evidence of estrogen deficiency. In each instance, treatment with estrogens resulted in prompt relief of the symptoms, paralleled by estrogenic changes in the vaginal smears.

In order to prevent recurrence of symptoms, it became our practice to place these patients on maintenance doses of estrogens. This was accomplished with intramuscular injections of estradiol benzoate or estradiol dipropionate, every two to four weeks, or with estradiol vaginal suppositories (2,500 R.U.), 2 or 3 times weekly. The dose of estrogens necessary to keep the patient adequately supplied varied in different patients and required individual adjustment. Vaginal smear examinations at intervals of two to four weeks were performed to insure the adequacy of the estrogen dose.

#### COMMENT

The orthodox treatment of functional disorders of micturition, with or without stress incontinence, in elderly women, which consists of bladder irrigations, silver nitrate instillations, etc., is frequently attended by poor or indifferent results. In 10 of the cases reported here, the urinary symptoms could not be accounted for on the basis of any demonstrable disease in the urinary tract. Six patients, however, had clinical evidence of obstetric trauma, viz., moderate cystoceles or urethroceles. The possibility of an anatomic lesion in the sphincter mechanism playing a role in the etiology of the urinary symptoms in this group cannot be excluded. However, it is noteworthy that the symptoms in these cases did not appear until after the menopause. This leads us to believe that if the anatomic lesions were involved at all in the genesis of these symptoms, they acted only in an accessory role. Furthermore, this study revealed the fact that 4 of the patients with incontinence were never exposed to the trauma of labor, 3 of them being virgins. This observation eliminates the possibility of ascribing the incontinence, in these cases, to an anatomic defect of the bladder sphincter resulting from parturition. It is evident, therefore, that urinary frequency, urgency, dysuria, and incontinence can occur in elderly women without evidence of organic disease or of anatomic defects in the urinary tract, and without exposure to the trauma of parturition.

This study disclosed one factor common to all of these cases, viz., morphologic evidence of estrogen deficiency. The striking results obtained with estrogen therapy, in the majority of these cases, and the recurrence of symptoms associated with re-appearance of signs of estrogen deficiency following estrogen deprivation, lead us to believe that estrogens play a role in the physiologic processes involved in normal micturition in women.

The question arises as to the *modus operandi* of the estrogens. The muscle fibers of the bladder sphincter are intimately related anatomically (and probably also embryologically\*) to the muscularis of the

\*The bladder appears to be formed partly from the ends of the Wolffian ducts and partly from the entodermal cloaca. According to Berry Hart, the lower third of the vagina is formed by the coalescence of the upper portion of the urogenital sinus and the lower ends of the Wolffian ducts, and the epithelial lining of the vagina is derived from the Wolffian bulbs.<sup>6</sup> It is tempting to believe that the bladder sphincter, which shares a common embryologic component with the vagina, may be under the influence of the same hormonal stimulus as the latter, viz., the estrogens.

# ROLE OF CARBON DIOXIDE IN RESUSCITATION AT BIRTH AFTER ASPHYXIA AND AFTER NEMBUTAL ANESTHESIA\*

AN EXPERIMENTAL STUDY IN THE CAT AND GUINEA PIG

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THE observations to be reported are part of a broader study of the physiology of respiration in the fetus and newborn. No attempt will be made to correlate the dosages of nembutal we have used with those commonly or uncommonly employed in the human being. From the standpoint of experimentation it is permissible and often desirable to study exaggerated effects; this we have done with no thought as to whether or not you might have occasion to employ comparable amounts of the drugs.

In February of last year Dr. Yandell Henderson addressed a letter to the Editor of the *Journal of the American Medical Association*, in which he proposed a new word in anesthesia. He suggested *anarchapnea*, containing the Greek roots "arehon" (governor) and "pneuma" (breath), to indicate a state of uncontrolled respiration encountered after excessive use of certain narcotic drugs, notably the barbiturates. The government of respiration by carbon dioxide appears to be abolished in deep barbiturate narcosis. The responsiveness of the respiratory center is lowered, the volume of breathing diminishes, hypereapnia manifesting itself as carbon dioxide displaces oxygen in lung alveoli, and anoxia ensues.

The use of carbon dioxide diluted in oxygen for resuscitation in asphyxia of the newborn has been debated for some years. One group of obstetricians report that they have used carbon dioxide advantageously, while another group holds that it is definitely contraindicated. Henderson suggested that both may be correct. Those who favor its use have employed no barbiturates or have used them sparingly. Those who have had adverse experiences with carbon dioxide have induced narcosis, often deeply, with the barbiturates, and the babies may well have been in a state of anareapnea in which carbon dioxide could not stimulate breathing.

We were particularly interested in Henderson's suggestions, because we had had some similar experiences in resuscitating newborn kittens, asphyxiated in the course of studying respiration during birth. Since then we have taken care to observe the effects of carbon dioxide in oxygen-air mixtures used to resuscitate after asphyxia and after barbiturate narcosis.

We have studied intrauterine respiratory activities in several hundred fetuses of several species during the last few years. Respiration at birth

\*Read at a meeting of the Chicago Gynecological Society, May 16, 1941.

an estrogen deficiency are found, such patients, regardless of the presence of an organic lesion (e.g., cystocele or urethrocele), should be given a therapeutic test with estrogens.

#### SUMMARY AND CONCLUSIONS

1. Sixteen postmenopausal women with urinary symptoms (urinary frequency, urgency, and incontinence), which were refractory to orthodox treatment, were found to have an estrogen deficiency.

2. Acting on the assumption that the urinary symptoms were related to the estrogen deficiency, these patients were treated with estrogens.

3. Relief of symptoms was achieved in all but 3 cases.

4. Relief of symptoms ran parallel with evidence of estrogenic effect in the vaginal smears.

5. Symptoms recurred gradually after the discontinuation of therapy, coincident with the re-appearance of signs of estrogen deficiency in the smears.

6. Patients could be kept symptom-free on a maintenance dose of estrogens.

7. On the basis of the observations reported here, it is concluded that: (a) a syndrome consisting of urinary frequency, dysuria, and incontinence in elderly women can be caused by a long-standing estrogen deficiency; (b) in advanced stages, the estrogen deficiency leads to atrophic erosions of the mucous membrane of the urethral meatus similar in appearance to the erosions in "senile vaginitis"; this "senile urethritis and periurethritis" causes urgency, painful micturition, and frequency; (c) the estrogen deficiency also leads to impairment of the bladder sphincter function which results in incontinence.

8. It is suggested, on the basis of these observations, that postmenopausal women, upon whom vagino- or urethroplasty is contemplated for the relief of incontinence, whether or not a cystocele or urethrocele is present, be examined for evidence of estrogen deficiency, and, if such a deficiency is found, that they be given a full course of estrogens as a therapeutic trial.

#### REFERENCES

- (1) *Salmon, U. J., and Frank, R. T.*: Proc. Soc. Exper. Biol. & Med. 33: 612, 1936. (2) *Geist, S. H., and Salmon, U. J.*: AM. J. OBST. & GYN. 38: 392, 1939. (3) *Frank, R. T., Goldberger, M. A., and Salmon, U. J.*: Proc. Soc. Exper. Biol. & Med. 33: 615, 1939. (4) *Fluhman, C. F., and Murphy, K. M.*: AM. J. OBST. & GYN. 38: 778, 1939. (5) *Salmon, U. J.*: Proc. Soc. Exper. Biol. & Med. 41: 515, 1939. (6) *Hart, B.*: Gray's Anatomy, ed. 21, 1216, Philadelphia, 1924, Lea & Febiger.

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Machado, Lucas M.: Tuberculosis of the Breast, Rev. de gynec. e. d'obst. 34: 326, 1940.

The author reviews the literature and presents a lengthy anatomic and pathologic discussion of the etiology of tuberculosis of the breast. It is suggested that radical mastectomy be performed for the primary type, the prognosis of which is good. In the secondary types, the treatment is general and palliative; the prognosis in this latter group is poor.

MARIO A. CASTALLO



lapse into apnea as it did in utero. It seems that the changed environment with markedly increased afferent stimulation lowers the threshold of the respiratory center.

When a cesarean section is performed in a decerebrated cat without general anesthesia and the uterine vessels are clamped to bring about anoxia in the fetus, the fetal heart beat slows to half or less than half its normal rate, motor activities are exaggerated and deep respiratory movements are initiated. These cause aspiration of the amniotic contents. Such an asphyxia can be prolonged in the cat for fifteen or twenty minutes and in the guinea pig for five to seven minutes. Respiratory movements become deep gasps at ten- to forty-second intervals. It has been our experience that the fetus must be delivered before these cease, to ensure spontaneous respiration. When this is done, breathing is established by the gasps, and normal respiratory movements are later superimposed upon the gasp rhythm as oxygenation of the blood takes place. Although no special measures were usually necessary, oxygen-air mixtures appear to speed resuscitation. When small quantities of carbon dioxide were added, the depth and sometimes the rate of the respirations were observed to increase. Recovery from simple asphyxia was usually complete within an hour or two in the cat, but symptoms of central nervous system damage, persisting for several days (even weeks in one case), were observed in a few animals, especially in the guinea pigs.

A very different picture of respiration at birth presented itself when nembutal was given to the mothers. The usual procedure was as follows: cesarean section was performed without anesthesia or under local anesthesia, and one fetus was delivered for control. It breathed at once. Nembutal was then administered intravenously to the mother. An anesthetic dose for adult animals was considered to be 28 mg. per kilo of body weight. In a few experiments, this amount was given. In some experiments as little as one-fourth of an anesthetic dose was used. Five minutes time was allowed between administering the drug and delivering the second and third fetuses. Following this, additional amounts of the drug were given (usually 7 mg. per kilo) and the remaining fetuses were delivered after another five minutes. In no experiment was more than a total of 28 mg. per kilo given.

After a full anesthetic dose of nembutal had been administered to the pregnant cats, the fetuses were profoundly narcotized. Some could not be induced to breathe. Others gasped feebly at rates of less than four times per minute. Most of them died within two hours. They were completely flaccid and appeared to draw little air into their lungs.

When approximately 20 mg. of the drug per kilo had been used, the fetuses were completely narcotized. They did not often begin to breathe for several minutes after delivery. Respirations then were gasps beginning slowly, and gradually increasing from two to about 10 or 15 per minute in the course of several hours. These gasps were less deep than those observed in nonnarcotized animals born after uncomplicated anoxia. They appeared to be less effective in drawing air into the lungs because hypotonus of the musculature did not allow adequate chest ex-

under normal and asphyxial conditions has engaged our attention in at least 50 litters of kittens and guinea pigs. The effects on the fetus of nembutal administered to the mother have been observed in 25 pregnant cats with 88 fetuses, for the most part within five days of birth, and about a dozen guinea pigs at full term.

A variety of experimental procedures have been used. The pregnant guinea pig lends itself well to operations after local anesthesia of the abdomen. This method cannot be used in cats successfully. It has been our practice to decerebrate most of these animals by ligating carotid and basilar arteries by the Pollock and Davis technique under ether an hour or more before starting to deliver their fetuses. This makes it possible to perform experiments on the fetuses without using anesthesia of any type.

Elsewhere we have described the physiology of respiration in utero at some length, but because it forms the basis for understanding our present subject we shall review it very briefly.

In the first place, a number of factors combine to insure an adequate supply of oxygen to the fetus. The blood reaching the fetal brain is rather well saturated with this gas throughout most of prenatal life. Upper limits of 90 per cent or more have been observed in experiments in sheep. Toward the end of gestation a physiologic partial anoxemia manifests itself as the efficiency of the placenta declines and fetal metabolic needs increase; the oxygen content of the blood going to the fetus decreases. It is erroneous, however, to conclude that a true anoxia is ever present, even at full term. In the cat, the partial anoxemia encountered at the end of gestation is relieved phasically by action of the uterine musculature.

In the latter part of gestation the cat fetus exhibits certain activities periodically as the uterine tonus waxes and wanes. With each uterine contraction the oxygen content of the blood passing from placenta to fetus rises, the fetal heart rate increases, fetal motor activities decrease and intrauterine respiratory movements are not observed. During the relaxed state of the uterus the oxygen content of the umbilical vein blood falls, the fetal heart rate declines, the fetus becomes active again, and occasionally brief, rapid rhythms of shallow, intrauterine respiratory movements occur. It is evident that these phenomena are associated with an anoxemia which is relieved by the contraction of the uterus, at least under conditions of experimentation with the animal's abdomen incised. To what extent they occur in the normal intact individual we do not know, but on only one occasion have we seen intrauterine fetal respiratory movements in an unanesthetized or unoperated cat and never in guinea pigs. Atmospheres low in oxygen or containing an excess of carbon dioxide when breathed by the mother do induce intrauterine respiratory movements in the apneic fetuses.

When a fetus is born normally or is delivered without anesthesia, the stimulus of the anoxia associated with interruption of placental exchange serves as an exaggeration of the stimulus of the intrauterine anoxemia associated with uterine relaxation; the fetal heart slows, the fetus squirms, and breathing starts at once. The blood becomes well oxygenated again due to pulmonary breathing, but the newborn does not

In attempting to interpret our results, the concept of Yandell Henderson is especially valuable. It would seem that excessive but subanesthetic doses of nembutal administered to pregnant cats and guinea pigs engendered states of anarachpnea in the fetuses. Delivery during the anarachpnea brought forth newborns which quickly became hypercapnic (i.e., their blood carbon dioxide level increased), and gasped only under the stimulus of anoxia. Administration of carbon dioxide only added to the hypercapnia and did not alter the respiratory response. In profound anarachpnea, air alone was insufficient for resuscitation, probably because the high content of carbon dioxide in the newborn lungs excluded oxygen (as the tension of one gas goes up the other must go down). During anarachpnea, oxygen administration was necessary to prevent asphyxia while the newborn was recovering from the narcosis.

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### DISCUSSION

DR. FRANKLIN F. SNYDER.—Dr. Windle has pointed out the dosage level at which deep depression and disorganization of respiratory regulation occur following intravenous administration of pentobarbital. In cats, it is stated that less than 30 mg. per kg. may result in depression of respiration to a level as low as 2 per minute. Normal oxygenation of the blood would be reduced in addition to the depression of the central nervous system.

At this level of activity of the respiratory system one is studying the abnormal and must be prepared for apparently paradoxical findings. This has turned out to be the case with regard to the administration of  $\text{CO}_2$  and oxygen. Marshall and Rosenfeld, in 1936, demonstrated that in cats deeply depressed by pentobarbital and anoxemic, the administration of 5 per cent  $\text{CO}_2$  in oxygen, instead of stimulating respiration, caused further depression or even apnea and death from respiratory failure. Under controlled conditions it was shown that oxygen, however, and not  $\text{CO}_2$  was responsible for this effect. It depended upon the fact that in animals, deeply depressed, respiration may be maintained almost entirely by an anoxemic stimulus, so that oxygen by removing this stimulus depresses or abolishes respiration.

Experiments on denervation and freezing of the sino-aortic mechanism indicated that administration of oxygen was equivalent to a removal of stimuli acting mainly, if not entirely, through this mechanism. When severe depression by oxygen was observed, the addition of  $\text{CO}_2$  to the oxygen failed to prevent this depression.

I cite these experiments to illustrate that different responses are elicited at different levels of respiratory activity corresponding to the degree of injury of the respiratory system. At the present stage of Dr. Windle's experiments, it seems to me that the role of  $\text{CO}_2$  in the final results still remains to be defined.

Dr. Windle mentioned also a state of uncontrolled breathing in the newborn as a result of narcosis. Another example of this interesting condition comes to mind. In normal rabbit fetuses delivered prematurely, Rosenfeld and I obtained kymograph tracings of respiratory activity at an early stage of development before regulation by  $\text{CO}_2$  and low oxygen was demonstrable.

DR. C. E. GALLOWAY.—In order to transfer these studies to practical use we could probably come to this conclusion: If we are dealing with a narcotized baby when we have used nembutal, it apparently will pay us to use oxygen instead of a mixture of oxygen and carbon dioxide.

Another point I gathered especially from Dr. Snyder's remarks is that when you are dealing with a premature baby, you should be careful about any anesthetic drug. Probably a local anesthesia would be better than a drug like nembutal that

pansion. Although some air did enter the lungs of most of them, normal rhythmical breathing did not usually occur until the narcosis had begun to subside. Some of these fetuses died in a cyanotic condition. They appeared to be asphyxiated in spite of their efforts to obtain air.

When one-fourth to one-half of an adult anesthetic dose of nembutal had been administered, the fetuses nearly always began to breathe within one or two minutes. Here too, respirations were slower than normal, often even slower than those of fetuses delivered after prolonged anoxia. The volume of breathing appeared to be lessened in the newborn under these dosages of nembutal. Initial respirations were not so deep as those encountered in the normal control animals.

The effects of nembutal upon the newborn cat and guinea pig fetuses lasted from several hours to two days, depending on the depth of the narcosis. Even when less than 14 mg. per kilo had been given to the mothers, the young animals did not begin to move about for an hour or more. Often they failed to nurse for the first day and probably obtained little nourishment for several days because of the residual lethargy.

As soon as possible after delivery and when it had become evident that the narcotized newborn animals had established regular, though often very slow rhythms of breathing, they were placed in warm chambers of 70 liters capacity. In one chamber, oxygen was added to the air; in another a mixture of oxygen (90 per cent) and carbon dioxide (10 per cent) was added. In a few experiments the carbon dioxide content was raised further by adding a small quantity of the undiluted gas to the latter mixture.

The mixtures of carbon dioxide in oxygen had no visible beneficial effect on the respiration of any narcotized cat fetus for the first hour or two after birth. A few of the guinea pigs, not so heavily narcotized and already executing more normal rhythms of breathing, did respond to the carbon dioxide. Heavily narcotized cat fetuses died when left in the carbon dioxide mixtures for several hours, although several recovered in atmospheres containing a high percentage of oxygen alone. Cyanosis was relieved and regularity of breathing improved as recovery from the narcosis gradually took place.

The newborn animals delivered after doses of about one-half anesthetic value were especially interesting. Litter mates were delivered simultaneously and placed in the warm chambers, one in oxygen-air mixture and the other in oxygen-carbon dioxide-air mixture. No difference in the rate or depth of their respirations could be observed for more than two hours. It was perfectly clear that their breathing was unaffected by the powerful respiratory stimulant, carbon dioxide. As soon as the narcosis began to subside and the animals began to move about, we could observe an increase in depth of respirations of the specimens in the carbon dioxide mixture. Later this was occasionally followed by an increase in the rate as well. The respirations of the animals in the oxygen-air mixtures increased in rate but decreased in depth at the time the narcosis subsided. Ultimately they became equal to those of the nonnarcotized control animals.

needle into the trachea and inflated the fetal lungs with oxygen, even though these animals may have been delivered for a number of minutes, they responded to the oxygen, began to breathe, and survived.

In regard to the relation of intrauterine respiratory movements to aspiration of amniotic fluid, and the effect aspiration may have on later ability of the child to breathe, I should say that in our experiments those newborn fetuses which had aspirated the amniotic contents nearly always showed râles in the chest which we could hear quite easily.

We do not hold that aspiration is a normal phenomenon in utero, and I think we have some good evidence that it is not. The lung of a full-term guinea pig fetus removed after clamping the trachea in utero to prevent aspiration has a glandular appearance. The lung of one allowed to execute strong intrauterine respiratory movements is partly expanded by the aspirated amniotic fluid and looks like the usual pictures of human stillborn lungs. In the lung of an animal born normally and allowed to breathe only five minutes, one sees many compact unexpanded regions like the truly atelectatic lung of the apneic full-term fetus.

## REACTIONS TO ESTROGENS

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IT IS generally assumed that only stilbestrol produces nausea and vomiting and that the use of the so-called natural estrogens (estradiol, estrone, and estriol) or their derivatives does not provoke these undesirable side reactions. In my belief such an assumption is erroneous. Several observers<sup>1, 2</sup> have noted that the acetylenic derivative of estradiol, ethynil estradiol, causes a high incidence of nausea and vomiting. In the reprints of the article by Shorr, Robinson and Papanicolaou on stilbestrol, the detailed data for each patient is tabulated (not presented in the article as published in the *J. A. M. A.*<sup>1</sup>). Seventeen of these patients were given natural estrogens (not including ethynil estradiol) in addition to the stilbestrol. Five of these 17 patients are listed by the authors as having undesirable side reactions after administration of estradiol benzoate or a preparation of mixed (estronelike) estrogens. One of these patients had nausea and a second had nausea and vomiting. In addition to the observations to be presented in this paper, the present author has noted nausea and vomiting in a patient following estradiol benzoate (2.0 mg.) and in 3 patients following estrone (2 after 20,000 I.U. and 1 after 5.0 mg. suspended in oil).

Studies have been made on the clinical effectiveness of various natural and stilbene estrogens. In the course of these studies, reactions (nausea and vomiting) have been observed to follow the administration of natural estrogens as well as after stilbene compounds. Observations on reactions following an esterified natural estrogen are presented in this communication and compared with those following two comparable stilbene compounds.

### REACTIONS TO ESTRADIOL CARBETHOXYLATE

Thirty-nine menopausal patients have been treated with parenteral estradiol carbethoxylate\* for a period varying from eight to twenty-four

\*Furnished through the courtesy of Drs. C. O. Miller and C. H. Mellish of Lakeside Laboratories.

causes depression of the respiratory center. In such a case we are apparently dealing with an individual who does not respond to respiratory stimuli in the same way that a full term baby does.

I am wondering what would happen to a baby if you gave the mother doses of nembatal equivalent in amount to those used on animals in these experiments five minutes before the baby was born. Twenty-eight to 30 mg. of nembatal per kilo of body weight means  $\frac{1}{2}$  gr. per kilo. My patients average 146 pounds at the time they deliver. That means if we give a woman 30 mg. per kilo we would give her about 36 gr. of nembatal. I am afraid this would kill the baby.

I would like to ask these men why they do not do experimental work with amounts of anesthesia in the animal comparable to those we used in practice. For instance, we get along very nicely with 6 gr. of nembatal in the average case. That amount constitutes about one-fifth to one-sixth of the dose used in these experiments.

There is one great fault with the barbiturates and that is the small margin between the anesthetic and the lethal dose. With intravenous anesthesia with barbiturates you had better have some method of artificial respiration ready. It is a dangerous anesthetic at the present time, and I think we should be very careful in using it, especially intravenously.

DR. WINDLE (Closing).—I think we have adequate controls in our present experiments because of the fact that in each experiment we delivered one fetus without anesthesia and without narcosis, and this served as control. The rest of them then were delivered under nembatal anesthesia or after asphyxia had been set up by clamping the umbilical or uterine vessels.

I am not quite sure how far we agree at present on the subject of intrauterine respiratory movements. We do agree on the fact that intrauterine respiratory movements can be obtained under certain conditions. Carbon dioxide certainly induces them in the apneic fetuses of the cat. I would like to ask how many obstetricians have actually seen these movements in the human being under normal circumstances. I have yet to find one who has seen them frequently. In fact, most men tell me that they have never seen them at all.

Dr. Galloway's practical interpretation is essentially correct. As I said in my preliminary remarks, we have no axe to grind in respect to the use of barbiturates in obstetrics. I do not know what would happen if you gave a mother 36 gr. of nembatal intravenously five minutes before the baby was born, but I expect that you would have a much depressed baby. We never used more than  $\frac{1}{2}$  gr. per kilo in any pregnant cat; usually half of this or less. The smallest total dosage was about equivalent to 7 gr. in a human being weighing 146 pounds. It is certainly true in the cat that when we gave a full anesthetic dose, we had great difficulty getting the newborn to survive. We have never lost a mother cat under those circumstances. The lethal dosage may vary for different animals and is about twice our anesthetic dosage for cats. Guinea pigs do not seem to be as much affected as cats.

The total blood volume of the human newborn has been found to be about 365 c.c. The oxygen capacity of the blood is approximately 21.5 volumes per cent. Utilization of oxygen (at least in the sheep fetus) is at the rate of 4.3 c.c. per kilogram per minute. If the blood of the newborn is 50 per cent saturated, there is a reservoir of about 40 c.c. of oxygen in the blood stream of the newborn. Thus a 3 kilogram baby would have a four-minute supply of oxygen. You know that babies do not die in four minutes of apnea.

That brings up another point, one that has been emphasized recently by Himwich. This investigator has shown that the survival time of the newborn rat is very long (fifty minutes) in comparison with the adult survival time (two to three minutes), but when he injected iodoacetate into the young rat, its survival time decreased to the adult survival time. Thus he gave us evidence that survival time is facilitated by anaerobic glycolysis in the newborn and does not depend entirely upon the amount of oxygen in the blood stream.

In regard to the question about the use of the tracheal catheter, I might say that we have performed a series of interesting experiments in guinea pig fetuses. After asphyxiating them until the respiratory movements stop in utero, we have not had one fetus start to breathe spontaneously thereafter. Yet when we put a hypodermic

dipropionate 6 (16.2 per cent) of the 37 patients had nausea and 7 (18.9 per cent) complained of reactions following estradiol carbethoxylate.

Twenty-nine of these same patients were given methyl stilbestrol subsequent to their treatment with estradiol carbethoxylate. The reaction incidence was about the same for these two substances (Fig. 1). Six of these 29 patients (20.7 per cent) had had reactions following the estradiol carbethoxylate, and after methyl stilbestrol 5 (17.2 per cent) had reactions.

The dosage range and average doses of the 3 estrogens used in this procedure are shown in Fig. 1. The data for estradiol carbethoxylate are presented for the 37 patients who received stilbestrol dipropionate and are also recalculated for the 29 patients who also received methyl stilbestrol. Each different dose received by an individual is included in calculating the "average dose." It is evident that estradiol carbethoxylate was given in doses similar (in mg.) to those of the stilbestrol dipropionate and smaller than those of the methyl stilbestrol.

#### COMMENTS

These data are not presented with the intention of condemning the particular esterified natural estrogen used in this study. It seems probable that a similar reaction incidence would follow the use of *comparable effective amounts* of any other natural estrogen.

The average individual dose of estradiol carbethoxylate given to the 39 patients (4.37 mg.) according to Fischer's data<sup>4</sup> is equivalent to 13.15 mg. (131,500 I.U.) of estrone or 6.12 mg. (61,200 I.B.U., or 36,720 R.U.\*) of estradiol benzoate. Judging from its clinical effectiveness the potency of estradiol carbethoxylate is somewhat less than this, but at any rate, the doses used in this study were at a level rarely approached in ordinary clinical practice.

There seems to have been little realization of the great potency of the doses of stilbestrol or related compounds used by many observers. It is difficult to express the potency of these compounds in terms of better known natural estrogens since various authors disagree in their determinations based on animal experiments. However, Shorr, Robinson and Papanicolaou<sup>1</sup> have presented data concerning the potencies of these various compounds in the human being. Calculating from their data, 1.0 mg. of parenteral stilbestrol has the same activity as 17,000 to 21,000 I.U. of parenteral estrone. To obtain the estrogenic effect of 5.0 mg. of stilbestrol one would have to give 85,000 to 105,000 I.U. of estrone in one single injection. The oral potency of stilbestrol is 50 to 100 per cent (average approximately 78 per cent) that of parenteral stilbestrol. The 2.0 to 4.0 mg. daily dose which these authors consider to be the "oral estrogenic unit" is therefore equivalent to the *daily injection* of somewhere between 26,000 and 63,000 I.U. of estrone.

The fact that reactions have not previously been associated to any great extent with the use of natural estrogens is understandable. These substances are very costly to prepare and have been furnished to the clinicians in dosage forms that are relatively minute when contrasted

\*1 mg. = 6,000 R. U.

weeks. The doses ranged from 1.0 to 10.0 mg. and averaged 4.37 mg. for the whole series. These dosages are obviously larger than those commonly used in clinical practice. They are comparable, however, to the amounts of stilbene estrogens which have been used by various workers.

Five of these 39 patients complained of nausea (12.6 per cent) and two of nausea and vomiting (5.3 per cent) following one or more treatments, a reaction incidence of 17.9 per cent during therapy with estradiol carbethoxylate. It is apparent that the production of nausea and vomiting is not a characteristic peculiar only to the stilbene estrogens, since these reactions also follow the use of this esterified natural hormone.

#### COMPARISON OF REACTION INCIDENCE PRODUCED WITH NATURAL AND STILBENE ESTROGENS

The reaction incidence with estradiol carbethoxylate is similar to that produced by comparable doses of an esterified stilbene in our hands. In a series of 136 menopausal patients reported elsewhere<sup>3</sup> stilbestrol dipropionate\* caused vomiting in 1.5 per cent of the patients and nausea

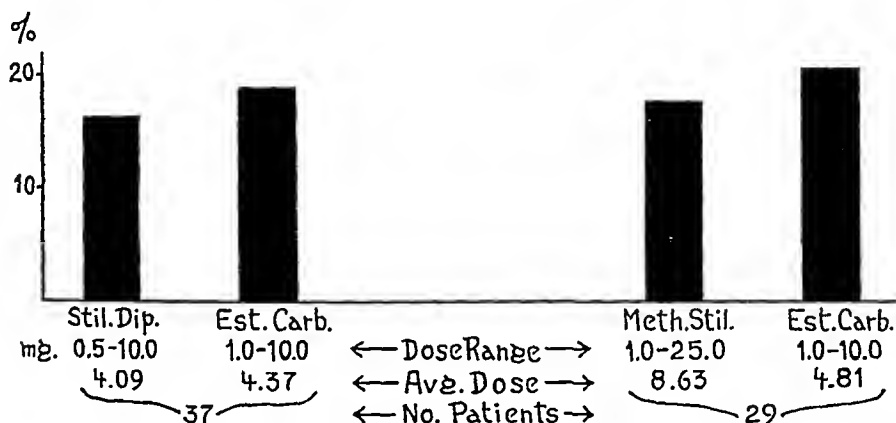


Fig. 1.—Reactions of patients to different estrogens.

(including those who vomited) in 14.7 per cent of the patients. In an incomplete study of the effectiveness of somewhat larger doses of methyl ether of stilbestrol,† data have been tabulated for 66 menopausal patients. Vomiting was produced in 3.0 per cent of these patients and nausea (including those who vomited) in 16.5 per cent of them.

A direct comparison of the natural and stilbene estrogens is possible since 37 of the patients given estradiol carbethoxylate had previously been treated with stilbestrol dipropionate. These patients were not selected; that is, no attempt was made to use only patients who had had no reactions to stilbestrol dipropionate. Estradiol carbethoxylate was given to successive patients whose necessary maintenance dosage of the stilbestrol dipropionate was judged to be established as accurately as is possible. This procedure was followed because our primary interest was to compare the clinical effectiveness of the two compounds.

In this group of patients there was little difference between the stilbestrol dipropionate and the estradiol carbethoxylate in the occurrence of reactions (Fig. 1). During the course of therapy with stilbestrol

\*Furnished through the courtesy of Doctors C. O. Miller and C. H. Mellish of Lakeside Laboratories.

†Furnished through the courtesy of Dr. Franz Schmelkes of Wallace and Tiernan Products, Inc.



## GYNECOLOGIC SURGERY UNDER LOCAL ANESTHESIA

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LOCAL anesthesia has been used for many years in this country in gynecologic surgery. There are those<sup>1-3</sup> who have strongly advocated its use and have employed it with satisfactory results. Bartlett<sup>4</sup> found a mortality rate from ether anesthesia of 0.15 per cent, or one case in 738. Rollison<sup>5</sup> encountered six deaths in 6,062 patients receiving a general anesthetic, but no anesthetic deaths in 1,981 cases receiving local anesthesia. Moreover, local anesthesia has been found to produce fewer pulmonary complications, reduce dehydration and acidosis as well as gastrointestinal disturbances.

Spinal anesthesia has its advocates and in some hands it can apparently be used with great safety. However, those who have studied large series of cases from many clinics are of the opinion that operations performed under spinal anesthesia carry a definite hazard. Babcock,<sup>6</sup> for example, in a series of 215,000 patients receiving spinal anesthesia, recorded 75 anesthetic deaths, or one in 2,867 cases. Bower et al.<sup>7</sup> after a careful study stated that, "spinal anesthesia is responsible for more deaths than any other anesthetic in proportion to the number administered."

We, at the New York Hospital clinic, have likewise been impressed with the advantages of local anesthesia. We began by using it only in cases having definite medical complications. These results were so satisfactory that its use was extended to include many uncomplicated cases and elderly women. We have been repeatedly impressed by its relative safety and by an apparent decrease in morbidity, shock, and blood loss. These latter points have never been properly analyzed in previous papers, nor has the problem of the aged gynecologic patient been properly considered. With this in mind, we have analyzed our results with local anesthesia.

### MATERIAL

This material was drawn from the records of the Gynecological Service of the Lying-in Hospital from January, 1936, to December, 1940, inclusive. These cases represent all the major gynecologic operations performed under local anesthesia from both the private and ward services during these years. The number of vaginal operations was 177, and the abdominal 23, a total of 200 cases (Table I). The control material consisted of 177 major vaginal and 100 major abdominal operations performed under general anesthesia. These were consecutive cases, but were limited so that the percentage of operations performed each year was the same for both types of anesthesia. This was necessary because the number of operations performed under local anesthesia steadily increased each year.

to those of stilbestrol and related compounds. The amounts in ordinary clinical usage are insufficient to cause such responses.

The toxic actions and pathologic changes which have been produced in experimental animals with stilbestrol have been mentioned in several clinical articles. The manner in which these references have been presented seems unfortunate to me. It is quite true that, if given in sufficient quantities, stilbestrol is capable of producing grave pathologic effects.<sup>5-8</sup> However, we believe it should have been emphasized that the doses necessary to produce these effects must be 3,000 to 3,000,000 times the physiologic dose in the animals concerned. Of even greater importance is the neglected fact that equally potent amounts of the natural estrogens are also toxic and cause similar pathologic changes.<sup>9-15</sup> These effects, therefore, are not peculiar to stilbestrol, but are characteristic of estrogens in general. The fact that tremendous overdoses of estrogens are capable of producing truly toxic effects in experimental animals is, however, not of clinical importance. There are few substances of therapeutic value which are not toxic when given in equally tremendous overdoses.

#### SUMMARY

An esterified natural estrogen, estradiol carbethoxylate, has been used in treating 39 menopausal patients. Thirty-seven of these patients had previously been given stilbestrol dipropionate. The incidence of undesirable side reactions was as high with estradiol carbethoxylate as with the stilbestrol dipropionate. Twenty-nine of these patients were given methyl stilbestrol subsequent to the estradiol carbethoxylate and showed approximately the same reaction incidence with both substances.

It is believed that nausea and vomiting are nonspecific responses which may be evoked by very high doses of natural as well as synthetic estrogens.

#### REFERENCES

- (1) Shorr, E., Robinson, F. H., and Papanicolaou, G. N.: J. A. M. A. 113: 2312, 1939. (2) Loesser, A. A.: Brit. M. J. 1: 13, 1939. (3) Greene, R. R., and Dorr, E. M.: J. Clin. Endocrinol. In press. (4) Fischer, A.: Arch. internat. de pharmacodyn. et de therap. 58: 332, 1938. (5) Varangot, J.: Presse méd. 47: 725, 1939. (6) Loesser, A.: Ztschr. f. d. ges. exper. Med. 105: 430, 1939. (7) Arnold, O.: Klin. Wchnschr. 18: 1891, 1939. (8) Tislowitz, R.: Acta brev. Neerland. 9: 15, 1939. (9) Arnold, O., Holtz, F., and Marx, H.: Naturwiss. 24: 314, 1936. (10) Selye, H.: Canad. M. A. J. 41: 48, 1939. (11) Burenther, A., and Schabbel, E.: Klin. Wchnschr. 16: 1667, 1937. (12) Baló, J. F., and Purjesz, B.: Klin. Wchnschr. 16: 1160, 1937. (13) Tislowitz, R.: Acta. brev. Neer. 8: 103, 1938. (14) Kochakian, C. D.: Endocrinology 26: 54, 1940. (15) Greene, R. R., and Burrill, M. W.: Unpublished observations.

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Calero, Carlos M.: Menstruation During Pregnancy, Rev. de gynec. e. d'obst. (Rio de Janeiro) 2: 69, 1940.

After reporting the medical history of a case, the author reviews the causes of hemorrhage during pregnancy. Going into details concerning all possible types of such hemorrhages including an analysis of chemic and cytologic changes in pregnant and menstruating women, he definitely concludes that the case presented is one of menstruation during pregnancy.

MARIO A. CASTALLO.

posited at this point, blocking the internal pudic nerve as it passes dorsal to the spine of the ischium just before entering Alcock's Canal. The needle is then withdrawn until it lies just beneath the skin. The direction is then changed laterally toward the tuberosity of the ischium, and the needle is then inserted until the point strikes the bone. Five cubic centimeters are injected while the needle is gradually withdrawn. This anesthetizes the large perineal branches of the posterior cutaneous femoris. The needle is again withdrawn until it lies just beneath the skin and its direction is changed vertically upward. While it is advancing, 5 c.c. is deposited in the subcutaneous tissue of the labium majus, blocking off the perineal fibers of the ileoinguinal nerve.

TABLE I. LIST OF OPERATIONS

OPERATION	NO. CASES
<i>General Anesthesia: A. Vaginal Operations</i>	
Anterior and posterior repair	71
Manchester operation and posterior repair	78
Vaginal hysterectomy	7
Repair of fistula	2
Amputation of cervix and posterior repair	10
Watkin's interposition and posterior repair	2
Excision of cervix	1
Repair of hernia of cul-de-sac of Douglas	2
Vulvectomy	1
Anterior and posterior repair and laparotomy	3
Total	177
<i>B. Abdominal Operations</i>	
Hysterectomy and salpingo-oophorectomy	57
Panhysterectomy	2
Uterine suspension	16
Myomectomy	8
Oophorocystectomy and appendectomy	15
Exploratory laparotomy	2
Total	100
<i>Local Anesthesia: A. Vaginal Operations</i>	
Anterior and posterior repair	77
Manchester operation and posterior repair	75
Vaginal hysterectomy	1
Repair of fistula	4
Amputation of cervix and posterior repair	3
Repair of third degree laceration	1
Watkin's interposition and posterior repair	1
Excision of cervix	1
Repair, hernia cul-de-sac of Douglas	1
Vulvectomy	3
Le Fort	10
Total	177
<i>B. Abdominal Operations</i>	
Hysterectomy	2
Panhysterectomy	1
Oophorocystectomy	7
Tubal ligation	2
Exploratory laparotomy	10
Abdominal and vaginal	1
Total	23

"The procedure is repeated on the opposite side, the operator using the same finger of the right hand. The vaginal mucosa and skin of the perineal area as high as the clitoris becomes anesthetized in five minutes. Relaxation of the levator ani and perineal muscles is usually complete at this time."

Some operators prefer to locate the ischial spines per vaginam rather than rectally thereby avoiding the rectum as a source of contamination. One per cent procaine

## METHODS

Whether a vaginal or abdominal operation is to be performed, the following preliminary medication is administered: Pentobarbital sodium 0.1 Gm. the night before operation and 0.2 Gm. an hour and one-half prior to operation, supplemented by morphine sulfate 0.010 Gm. and scopalamine hydrobromine 0.0004 Gm. one hour later.

The technique for local pudendal and perineal block anesthesia is essentially that described by Urnes<sup>8</sup> (Fig. 1).

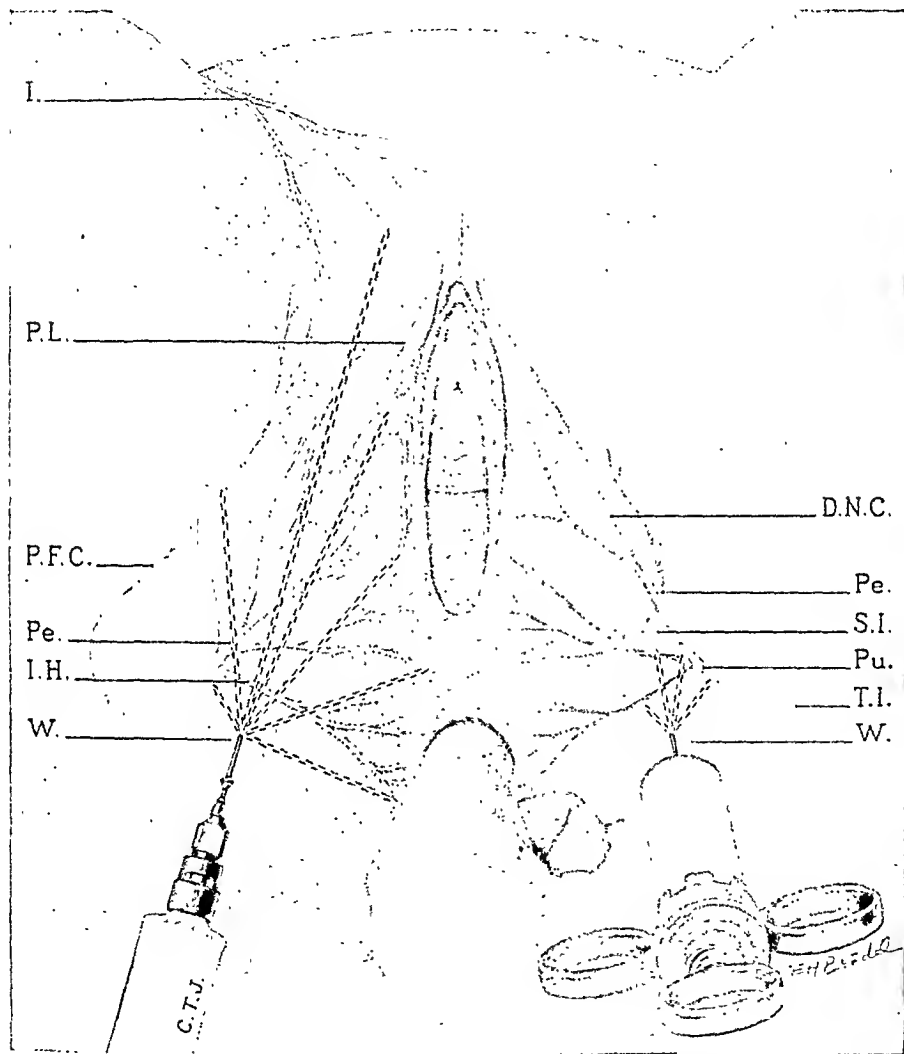


Fig. 1.—Diagram showing local infiltration technique of the nerves of the female perineum. Superficial and deep innervation is shown on the right and left sides of the patient, respectively. *I.*, Ilioinguinal nerve; *P.L.*, posterior labial nerve; *P.F.C.*, posterior femoral cutaneous nerve, perineal branch; *Pe.*, perineal nerve; *I.H.*, inferior hemorrhoidal nerve; *D.N.C.*, dorsal nerve of clitoris; *Pu.*, pudendal nerve; *S.I.*, spine of ischium; *T.I.*, tuberosity of ischium; *W.*, wheal, intradermal.

With the patient in the exaggerated lithotomy position, intradermal wheals are made bilaterally, halfway between the rectum and the tuberosity of the ischium. The anesthetic used is 0.5 per cent procaine. The index finger is inserted into the rectum to palpate the ischial spines. A 10 cm. needle is passed horizontally through the cutaneous wheal directly to the spine, and is allowed to slip just under and beyond it. Because of the direction of the needle and the guiding finger in the rectum, there is no danger of piercing the rectum. From 10 to 15 c.c. of solution is de-

ing the convalescent period. By morbidity is meant a temperature rise to 38.0° C. (100.4° F.) on any two postoperative days excluding the day of operation, from the first to the tenth day, temperatures being taken orally every six hours.

TABLE III. POSTOPERATIVE COMPLICATIONS

LOCAL ANESTHESIA		GENERAL ANESTHESIA	
<i>Vaginal Operations (177 Cases)</i>		<i>Vaginal Operations (177 Cases)</i>	
Febrile	22.5%	Febrile	32.2%
Postoperative shock	7.9	Postoperative shock	17.6
Urinary tract infection	13.6	Urinary tract infection	13.0
Respiratory infection	3.9%	Respiratory infection	1.2%
Deaths (1)		Deaths (0)	
<i>Abdominal Operations (23 Cases)</i>		<i>Abdominal Operations (100 Cases)</i>	
Febrile	39.1%	Febrile	43.0%
Postoperative shock	4.3	Postoperative shock	4.0
Urinary tract infection	8.7	Urinary tract infection	1.0
Respiratory infection	8.7%	Respiratory infection	7.0%
Deaths (1)		Deaths (1)	
<i>Total Cases (Abdominal and Vaginal: 200 Cases)</i>		<i>Total Cases (Abdominal and Vaginal: 277 Cases)</i>	
Febrile	24.5%	Febrile	36.1%
Postoperative shock	7.5	Postoperative shock	12.6
Urinary tract infection	13.0	Urinary tract infection	8.7
Respiratory infection	4.5%	Respiratory infection	3.2%
Deaths (2)		Deaths (1)	

There were three deaths (Table III) in the entire series. Of these, only one could be attributed to the anesthetic, which was in this particular case, gas-oxygen-ether. This patient died on the operating table, apparently of respiratory collapse, directly after opening the abdomen. The two other deaths occurred during the convalescent period and were in patients in whom local anesthesia had been used. There is, however, no evidence to indicate that either of these deaths were associated with the anesthetic agent. One patient died on the second postoperative day of advanced carcinomatosis and heart disease, the other died on the fourteenth postoperative day following a pulmonary embolus after an afebrile course.

#### CASE REPORTS

CASE 1.—(No. 157934). The patient was a 35-year-old colored female admitted to the Lying-in Hospital with a diagnosis of myoma uteri. Her general physical examination was entirely normal. Blood pressure was 140/90, with the cardiac findings otherwise not remarkable. A supravaginal hysterectomy was recommended. After routine preoperative analgesia of morphine and atropine, the anesthetic was begun. Nitrous oxide-oxygen mixture, administered by the closed method was used for the induction, this being supplemented by ether. The operation had proceeded as far as division of the round ligaments and clamping of the uteroovarian ligament on one side, when respirations ceased. Artificial respiration and stimulants produced no response. She received a total of 30 c.c. of ether, the duration of the anesthetic being forty-two minutes, the operating time fifteen minutes. The clinical cause of death was nitrous oxide-ether narcosis with respiratory collapse. Autopsy was obtained and showed no significant lesions.

is used in some instances instead of 0.5 per cent. In selected cases epinephrine is added to control bleeding and to prolong the anesthetic. To avoid injection of the solution into the blood stream, constant movement of the needle is necessary.

Anesthesia for abdominal operations is obtained by the systematic infiltration of a procaine solution in the skin of the abdominal wall beginning in the midline and extending laterally for a distance of 4 or 5 cm. After a period of three to five minutes, the skin and subcutaneous tissue to the fascia of the recti are incised. In a similar manner, the fascia is infiltrated and the muscle, if desired. The parietal peritoneum is infiltrated in the midline and to either side prior to incision, the thin filmy layers standing out in relief when the solution is gently injected. Further infiltration of the round, broad, and uterosacral ligaments and the visceral peritoneum may be carried out, depending on the extent of the operation. Two hundred to 300 c.c. of procaine is usually sufficient to produce a satisfactory anesthetic. Retractors should be avoided, tissues should be handled as gently as possible and packs should be used only when absolutely necessary.

#### ANESTHETIC RESULTS

We have attempted to evaluate the results of the anesthesia in the following manner: Grade 1, an entirely satisfactory result. Grade 2, a partially satisfactory result, the procaine affording satisfactory relief of pain for at least one hour but requiring an inhalation anesthetic thereafter. Grade 3, a failure.

We obtained Grade 1 anesthesia in 82.8 per cent (Table II) of the 177 major vaginal operations, 6.7 per cent Grade 2 results, and 10.1 per cent Grade 3, or failures, a result which compares favorably with Mathews,<sup>9</sup> who in 443 major and minor vaginal operations, obtained 70 per cent excellent results, 28 per cent good results, and 1.8 per cent failures. Gellhorn<sup>1</sup> also using the infiltration technique, rather than the pudendal block, obtained 64.5 per cent excellent results, 31.5 per cent good results, but requiring supplementary inhalation anesthesia, and 4 per cent failures in 82 cases of vaginal hysterectomy.

In 23 abdominal operations, we were able to obtain similar results to those obtained in vaginal operations, with 78.3 per cent, Grade 1, 13 per cent Grade 2, and 8.7 per cent failures. In both series, not a single instance of sensitivity to procaine was encountered.

TABLE II

<i>Local Vaginal Operations (177 Cases)</i>		
Anesthetic results:	Grade 1	82.8%
	Grade 2	6.7%
	Grade 3	10.1%
<i>Local Abdominal Operations (23 Cases)</i>		
Anesthetic results:	Grade 1	78.3%
	Grade 2	13.0%
	Grade 3	8.7%
<i>All Local Operations (200 Cases)</i>		
Anesthetic results:	Grade 1	82.5%
	Grade 2	7.5%
	Grade 3	10.0%

#### POSTOPERATIVE COMPLICATIONS

In the analysis of postoperative results, we have attempted to determine the mortality, morbidity, and other significant complications dur-

## PREOPERATIVE COMPLICATIONS

Any consideration of postoperative morbidity and mortality must be interpreted in the light of the preoperative condition of the patient. Hypertensive cardiovascular disease was found in 45.7 per cent of the patients having vaginal operations under local, but in only 5.8 per cent of those receiving a general anesthetic (Table IV). This diagnosis was corroborated in each incidence by a medical consultant. Similarly, the other forms of heart disease were likewise more frequent in the former group. Diabetes was noted in 8.5 per cent of the patients receiving procaine while being present in 1.69 per cent of the general vaginal patients. Respiratory disease occurred in 12.9 per cent of the former and 2.25 per cent of the latter. Urinary tract disease was not a common finding in these patients preoperatively, for it was not observed in a single patient receiving a general anesthetic and in only 2.8 per cent of the other group.

TABLE IV. PREOPERATIVE COMPLICATIONS

	HYPERTENSIVE CARDIO- VASCULAR DISEASE	OTHER CARDIAC DISEASE	BLOOD PRES- SURE 140/90 OR +	RESPIR- ATORY DISEASE	DIABETES	ANEMIA
General abdominal (100 cases)	4.0%	1.0%	10.0%	3.0%	5.0%	2.0%
General vaginal (177 cases)	5.8	0.56	20.3	2.25	1.69	1.68
Local abdominal (23 cases)	34.7	13.0	60.8	8.6	4.3	8.6
Local vaginal (177 cases)	45.7%	4.5%	61.0%	12.95%	8.5%	1.12%

## THE AGED PATIENT

It has been shown that the life expectancy of the general population has steadily increased, necessitating, therefore, the care of patients of more advanced years. Recent releases from the Bureau of Census based on the 1940 decennial census reveals<sup>10</sup> that, "The median age of the population of the United States increased to 28.9 years in 1940, from 26.4 years in 1930. Furthermore, the persons 65 years of age and over now number 8,956,000, an increase of 35 per cent over the number in this group in 1930." Through the medium of local anesthesia, we have been able to reduce the risk of operative complications in aged individuals. In recent years, we have operated upon many elderly women whom previously we should have turned away as too great risks. The average age of the patients operated upon under local anesthesia was 53 years, while those of the control group averaged 41.5 years (Table V).

TABLE V

OPERATIONS	CASES	AVERAGE AGE
General abdominal	100	35.84 years
General vaginal	177	44.7 years
Local abdominal	23	47.2 years
Local vaginal	177	53.8 years
Average age for group: 46.4 years.		
Average age for all locally anesthetized patients: 53.0 years.		
Average age for all generally anesthetized patients: 41.5 years.		

CASE 2.—(No. 260072). The patient was a 70-year-old, white woman who was admitted to the Gynecological Service with a diagnosis of probable carcinoma of the ovary. She presented, in addition, hypertensive cardiovascular disease (blood pressure 180/100) and a microcytic hypochromic anemia (hemoglobin 7.0 Gm.). Medical consultation was obtained and although the patient was considered to be a poor operative risk, laparotomy under local anesthesia for the investigation of the pelvic mass was deemed advisable. A blood transfusion was given preoperatively and preoperative medication included pentobarbital sodium 0.1 Gm., morphine sulfate 0.010 Gm., and scopolamine hydrobromide 0.0003 Gm. Procaine 1 per cent was used for infiltration of the anterior abdominal wall. The pathology was found to be an advanced ovarian malignancy and after biopsy of a small portion of the omentum, the incision was immediately closed. The operation lasted forty minutes, and the patient's condition was good throughout. The patient's course was steadily downhill after the first day postoperative. While receiving a transfusion on the second day, the patient died. The blood was re-matched and was found to be compatible. Death was considered to be due clinically to heart failure. Autopsy confirmed the findings of advanced serous cystadenocarcinoma of the ovary with multiple metastases together with thrombi in the right auricle and ventricle.

CASE 3.—(No. 260750). The patient a 62-year-old, Jewish housewife, was admitted to the Gynecological Service with a diagnosis of cystocele, rectocele, and hypertensive cardiovascular disease. Blood pressure was 160/110. The remainder of the physical and laboratory studies were not remarkable. A dilatation and curettage, cervical polypectomy and an anterior and posterior colporrhaphy were performed, using 1 per cent procaine, local pudendal block anesthesia. The patient withstood the procedure well. On the day of operation, the temperature rose to 38.0° C., this being the only day on which she had fever. She was allowed out of bed on the morning of the fourteenth postoperative day without apparent ill effects. During that afternoon, she was again allowed up, and while standing beside her bed, she collapsed. Routine stimulants and artificial respiration were of no avail and the patient died within fifteen minutes. The clinical cause of death, confirmed by autopsy, was pulmonary embolus originating from a pelvic thrombophlebitis.

The morbidity rate in the group of patients operated upon under local anesthesia was 24.5 per cent, as compared with 36.1 per cent for those patients receiving general anesthesia (Table III). This reduction in morbidity is all the more significant when it is realized that those patients receiving procaine anesthesia were poorer risks than those operated upon under general anesthesia.

The number of patients developing postoperative shock was substantially decreased by local anesthesia, 7.5 per cent developing shock as compared with 12.6 per cent in the general group. This may be partially explained by a decrease in blood loss although the actual measurement of blood was not carried out.

Respiratory disease occurred postoperatively in 4.5 per cent of those patients receiving local as compared with 3.2 per cent of those receiving general anesthesia. The incidence of respiratory disease preoperatively, however, was 12.5 per cent in the former but only 2.5 per cent in the latter.



## TWIN PREGNANCIES IN THE SERVICE OF THE CHICAGO LYING-IN HOSPITAL

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TWINS are of perennial interest not only to the obstetrician who delivers them but also to the embryologist, geneticist, or any scientist who may have an opportunity to observe them. The obstetrician is well aware of the dangers to the fetus and the increase in maternal complications which frequently occur with multiple pregnancies. The present series covering a period of ten years furnishes additional data on the probability of premature birth, maternal complications, and fetal and neonatal death.

From the opening of the present Chicago Lying-in Hospital May 25, 1931, until Jan. 1, 1941, there were 25,583 women delivered in the hospital and 5,548 by the Home Service Department. Among those in the hospital there were 281 who had twin pregnancies, and 2 who had triplets; of the home deliveries 52 had twins, none triplets. This is an incidence of 1:91 for twins among women in the hospital, 1:106.6 for women delivered at home, and 1:93.4 for the total 333 twin pregnancies. The incidence is slightly lower than that for the country as a whole. In the United States registration area, approximately one in every 87 pregnancies results in a multiple birth.<sup>1</sup>

Three of the mothers in the hospital and one mother at home delivered one reportable infant and one whose size and weight placed it in the nonreportable group (abortions). In addition, one patient had one fetus in the uterus and one in the Fallopian tube. Since the conditions surrounding the fetus in utero were those of a single pregnancy this case is omitted from the following discussion, and the figures are based on 332 twin pregnancies with 660 reportable infants.

A complete record of the incidence of twins among abortions in which the larger fetus weighed less than 400 Gm. is not available. Among approximately 1,200 abortions, however, there are one known set of triplets and at least 12 pairs of twins.

*Previous Pregnancies.*—Only 29.6 per cent (98) of the women in this series were primigravidas, in comparison to 42 per cent of primigravidas among the total number of women delivered at home and in the hospital during the same period. The remaining 70 per cent of patients with twins were distributed as follows: second pregnancy 25.3 per cent (84), third pregnancy 19.2 per cent (64), fourth pregnancy 8.1 per cent (27), and in the fifth to eleventh pregnancies 17.8 per cent (59). The average number of previous pregnancies was 1.89 for all patients with an average of 0.31 (16.5 per cent) of these ending in abortions. The 104 abortions occurred among 92 women, only 27.7 per cent of those in this series having had one or more pregnancies which terminated in this manner.

It is of interest that we found a total of 57 patients over 60 years of age, 7 of these having passed 70, all operated upon under local anesthesia without a single anesthetic death and with a morbidity rate of but 12.7 per cent.

#### SUMMARY

1. A total of 200 major gynecologic operations were performed without reaction to procaine.

2. In the same series, there were two deaths during the postoperative period, neither attributable to the anesthetic agent.

3. In a control series operated upon under general anesthesia, there was one anesthetic death considered due to nitrous oxide-ether narcosis.

4. The morbidity rates for the local and general anesthesia series were: 24.5 per cent and 36.1 per cent, respectively.

5. Postoperative shock was reduced from 12.6 per cent using general anesthesia to 7.5 per cent using local.

6. Respiratory infections occurred postoperatively in 4.5 per cent of the local group as compared with 3.2 per cent of the general series. However, the incidence of respiratory disease in the former was 12.5 per cent and 2.5 per cent for the latter preoperatively.

7. Urinary tract disease occurred postoperatively in 13.0 per cent of patients receiving procaine anesthesia as against 8.7 per cent of those receiving general anesthesia. However, 3.5 per cent of the local group had urinary tract pathology prior to operation, but none of the patients operated upon under general anesthesia were so affected.

8. The average age of patients operated upon under local was 53.0 years, while those of the control group averaged 41.5 years.

9. Fifty-seven patients over 60 years of age were operated upon, using procaine anesthesia, without an anesthetic death, and with a morbidity rate of 12.7 per cent.

#### CONCLUSIONS

Any type of gynecologic vaginal operation can be satisfactorily performed under perineal-pudendal block local anesthesia with reduction of the mortality and morbidity. Gynecologic abdominal surgery performed under local anesthesia, while less satisfactory in general, may be used advantageously in selected cases.

Local anesthesia by its safety has extended the scope of surgery and is the method of choice for anesthesia in the elderly woman.

We wish to express our appreciation to Dr. H. J. Stander whose interest and encouragement have made this study possible, and to Miss Elizabeth Broedel for her excellent illustration of the technique employed.

#### REFERENCES

- (1) Gellhorn, G.: J. A. M. A. 61: 1354, 1913; Surg., Gynec. & Obst. 45: 105, 1927; Ibid. 51: 484, 1930. (2) Greenhill, J. P.: J. A. M. A. 102: 28, 1934. Inter. Clin. 4: 171, 1925. (3) Fall, F. H.: AM. J. OBST. & GYNEC. 3: 400, 1922; 20: 310, 1930. (4) Bartlett, M. K., and Simmons, F. A.: Surg., Gynec. & Obst. 55: 777, 1932. (5) Rollison, J. W.: M. J. Australia 2: 580, 1929. (6) Babcock, M. E.: Anesth. & Analg. 11: 184, 1932. (7) Bower, J., Clark, J. H., and Burns, J. C.: J. A. M. A. 100: 245, 1933. (8) Urnes, M., and Timmerman, J.: Ibid. 109: 1616, 1937. (9) Mathews, H. B., and Mazzola, V. P.: N. Y. State J. Med. 37: 1, 1937. (10) Editorial, J. A. M. A. 116: 1526, 1941.

The average difference between the weights of the 2 fetuses is shown in Table II. When the larger fetus weighs between 2,000 and 3,500 Gm., the smaller fetus weighs about 12 per cent less. In fetuses weighing less than 2,000 Gm., the difference is proportionately somewhat less, in fetuses over 3,500 Gm. the difference is somewhat greater.

Of reportable twin infants, 49.4 per cent were at term according to weight in contrast to 94.8 per cent which were at term among 1,000 unselected single infants from this hospital.

TABLE I. WEIGHT IN RELATION TO LENGTH OF GESTATION

LENGTH OF GESTATION FROM FIRST DAY OF LAST MENSTRUAL PERIOD	SINGLE PREGNANCIES 1,000 CASES			TWIN PREGNANCIES 332 CASES		
	PREG. %	MEAN WEIGHT	COEF- FICIENT OF DEVI- ATION	PREG. %	MEAN WEIGHT	COEF- FICIENT OF DEVI- ATION
Total pregnancies	100	3405.8	157.2	100	2391.5	204.9
Term (265-295 days)	77.55	3418.3	140.6	52.81	2706.0	107.1
200-209	----	----	----	2.15	1650.0	139.5
210-219	----	----	----	2.33	1565.3	196.9
220-229	0.7	2716.6	152.3	5.57	2157.1	136.5
230-239	0.6	2050.0	238.0	7.36	1900.0	281.9
240-249	1.92	2923.6	121.1	10.05	2300.9	299.5
250-259	2.43	3133.3	180.2	14.54	2388.7	144.5
260-269	9.5	3098.9	142.7	19.56	2553.7	124.7
270-279	27.4	3325.0	136.9	25.68	2724.6	137.7
280-289	31.85	3591.0	122.3	10.59	2767.2	143.3
290-299	19.21	3618.6	131.6	2.16	2975.0	193.4
300-309	4.15	3650.0	110.8	0	0	----
310-319	1.84	3556.0	104.8	0	0	----
320+	0.40	3777.0	130.4	0	0	----

TABLE II. LENGTH OF GESTATION IN RELATION TO WEIGHT AT BIRTH

WEIGHT IN GRAMS	SINGLE PREGNANCIES			TWIN PREGNANCIES				
	PREG. %	MEAN LENGTH OF GESTA- TION	COEF. OF DEV.	PREG. %	MEAN LENGTH OF GESTA- TION	COEF. OF DEV.	AV. DIF. IN WEIGHT OF FIRST AND SEC- OND TWIN*	COEF. OF DEV.
Total pregnancies	100.0	281.7	12.4	100.0	256.2	25.4	--	--
Term (over 2,500 Gm.)	94.8	282.4	12.5	47.3	268.8	13.3	--	--
1-499	0.0	--	--	1.2	--	--	--	--
500-999	0.0	--	--	4.7	--	--	--	--
1,000-1,499	0.2	--	--	5.2	225.7	8.3	--	--
1,500-1,999	0.4	243.7	11.4	15.6	246.6	6.6	162.5	30.0
2,000-2,499	3.6	259.4	15.1	25.9	258.6	5.3	278.6	199.5
2,500-2,999	14.2	275.6	14.9	32.0	267.3	12.7	322.8	280.6
3,000-3,499	41.5	282.8	12.9	13.9	271.1	13.9	437.7	100.2
3,500-3,999	30.1	285.2	11.6	1.5	281.4	6.4	825.0	299.0
4,000-4,499	8.7	287.2	11.3	--	--	--	--	--
4,500 or over	1.3	292.1	5.4	--	--	--	--	--

\*The larger of the two infants determined the grouping.

*Length of Gestation.*—Calculated from the first day of the last menstrual period the average length of gestation in the 1,000 unselected single pregnancies mentioned above was 281 days. The average length of gestation in all of the twin pregnancies was 256 days. There is a much greater variation in the length of gestation in twin than in single pregnancies. Seventy-seven per cent of the single infants were delivered within fifteen days of the calculated term date (265 to 295 days from the

Two women had successive sets of twins, one in the first and second pregnancies, one in the seventh and eighth pregnancies, both of which are included in this series; two had twin pregnancies which were not successive (second and fourth, and unknown and ninth) and only one set of each is included. In most instances a definite history of the occurrence of twins among the relatives of the patient is lacking. In the triplet abortions, not included in this series, the siblings of the patient include two sets of twins.

*Birth Weight.*—The State of Illinois requires registration of all births and stillbirths in which the infant is advanced to the fifth month of gestation. Since the calculated gestational age is often inaccurate if based only on menstrual history, it seems more desirable to use a classification including weight and length in addition to menstrual age. All babies born in this hospital are grouped according to these three criteria, and this classification, having been given in several previous publications,<sup>2-4</sup> will not be repeated. Since practically all infants born before the end of the seventh lunar month fail to survive (weight at this time about 1,000 Gm.) these infants are separated into a special group which must be reported in mortality statistics even though they cannot be expected to live. An average of 35 per cent of those between 1,000 Gm. and 1,500 Gm. will survive, and it does not seem justifiable to consider, as do many authors, 1,500 Gm. as the lower limit of viability. In this paper those below 400 Gm. are considered as abortions, 400 to 1,000 Gm. as previable; 1,000 to 2,500 Gm. as premature and those over 2,500 Gm. as at term. Forty-three and six-tenths per cent of the twins were premature in contrast to 5.83 per cent of single pregnancies, and 5.2 per cent were previable in contrast to 0.52 per cent of single pregnancies occurring in this hospital. In his series of 503 twin infants over 1,500 Gm., Guttmacher<sup>5</sup> states that 56 per cent were of term weight, 44 per cent premature, but over 1,500 Gm. In the present series 53.3 per cent of the twins over 1,500 Gm. weighed over 2,500 Gm.

Dividing the twins into those delivered in the hospital and at home, it is interesting to note the higher incidence of infants weighing more than 2,500 Gm. among those delivered at home; in the latter group 64.5 per cent were over 2,500 Gm., in those delivered in the hospital only 49.4 per cent.

The average birth weight of 1,000 single infants delivered in this hospital was 3,405 Gm.; for this entire group of twins the average weight was 2,391 Gm., the latter having a birth weight only 70 per cent as great as that of an infant which has not shared the uterine cavity with another. Among these 1,000 infants, the average birth weight of those in which the length of gestation was considered as being at term (767 infants with a period of gestation of 265 to 295 days) was 3,418 Gm.; the average birth weight of twins at term (219 infants) was 2,706 Gm., the latter being 82 per cent of the former. The difference between 70 per cent in all pregnancies and 82 per cent in infants delivered within two weeks of term is accounted for by the greater incidence of the premature onset of labor among twin than among single pregnancies. The average weight together with the degree of variability and the percentage of cases falling in each group are shown in relation to the length of gestation in Table I. Daiser<sup>5</sup> in his group of 489 twins found that twins tended to weigh more than single fetuses until about the two hundred and thirty-fifth day of gestation, during the next two weeks they were about equal in weight, and from then on until 280 days the weight of the twins was proportionately less. This was not borne out in the present series, the twins having a consistently lower mean weight than that of the single fetuses of corresponding gestational age.

In 118 pregnancies both infants were at term according to weight; the one weighed more than 2,500 Gm. and the other between 1,000 and 2,500 Gm. in 83; one weighed over 2,500 and the other less than 1,000 in 3; and one was at term, the other an abortion in one case. In 102 pregnancies, both were in the premature weight group, in 13 both were previable, in 2 one was in the premature, the other in the previable group, in 3 one was in the previable group, the other in the group of abortions. In 2 cases each, one infant was at term and the weight of the other unrecorded, one was premature and the other unrecorded, and in 4 the weights of both infants were unrecorded. The total infants at term numbered 325, premature 290, previable 34, abortions 4, unrecorded 11.

among twins in 15.3 per cent; breech delivery in 3.2 per cent, among twins in 25.1 per cent; version and extraction in 0.8 per cent, among twins in 17.5 per cent; cesarean section in 4.5 per cent, among twins in 6.6 per cent. Of the total 256 versions and extractions, 115 (45 per cent) were performed for the delivery of second twins.

*Mortality in Relation to Time of Death.*—Among the 332 twin pregnancies, there were 28 (8.4 per cent) mothers who had neither baby living ten days after confinement, 36 (10.8 per cent) who had only one, and 268 (80.8 per cent) who had two living. There was a total mortality among the 664 offspring of 13.8 per cent (92), divided into 56 (59.8 per cent) neonatal deaths, 32 (35.9 per cent) stillbirths and 4 (4.3 per cent) abortions. These were divided into first and second twins as shown in Table IV.

TABLE IV. MORTALITY IN RELATION TO TIME OF DEATH

Stillbirths:	
Both stillborn	6
First living; second stillborn	12
Second living; first stillborn	7*
Neonatal deaths:	
Both died	16
First living; second died	12
Second living; first died	5
Neonatal death and stillbirth:	
First died; second stillborn	4*
Second died; first stillborn	2

\*Includes two abortions (stillbirths).

The total mortality for the first born of twins is 12.0 per cent (25 neonatal deaths, 15 stillbirths), for the second born 15.6 per cent (30 neonatal deaths, 22 stillbirths). If, however, only the viable, nonmacerated fetuses and infants are considered, the mortality rates for first and second twins are almost identical as there are 21 such first born twins and 22 second born twins.

*Mortality in Relation to Weight.*—The total mortality among twins in which at least one twin had reached a reportable age was 13.8 per cent (Table V); this is over three times the mortality for total pregnancies which, during the same period, was 4.3 per cent. The higher total mortality rate is due to the larger number of previable fetuses and the greater proportion of viable premature infants than is found in the total deliveries. The general mortality for infants weighing over 2,500 Gm. is 1.9 per cent and for twins is slightly higher (2.4 per cent). The total hospital rate, however, for the viable premature infants (1,000 to 2,500 Gm.) is almost twice (32.6 per cent) that for twins of similar weight (19.6 per cent). This is largely accounted for by the greatly decreased incidence of stillborn fetuses in this weight group (15.2 per cent of all infants, 5.5 per cent of twins), although there is also a slightly lower incidence of neonatal deaths (17.4 per cent of all

TABLE V. MORTALITY IN RELATION TO WEIGHT

WEIGHT IN GRAMS	TOTAL BIRTHS	NEONATAL DEATHS	STILLBIRTHS	TOTAL NUMBER	MORTALITY PER CENT
2,500 and over	325	6	2	8	2.4
2,000-2,499	175	1	5	6	3.4
1,500-1,999	83	9	5	13	15.4
1,000-1,499	32	17	6	24	75.0
400-999	34	20	14	34	100.0
Under 400	4	1	3	4	100.0
No record	11	1	2	3	
Total	664	55	37	92	13.86

first day of the last menstrual period). Among twins only 52.8 per cent were delivered within this same period. The majority of twins (87 per cent) were delivered before 280 days while less than half of single infants were delivered before the same date.

The average length of gestation for infants in single pregnancies in which the birth weight was within the range considered as normal for an infant at term (2,500 to 4,500 Gm.) was 282.4 days. The average length for infants in twin pregnancies for the same weight group was 268.8 days, or an average of fourteen days less than in single pregnancies. Part of this may be accounted for by the proportionately greater number of twin infants in the lower weight groups, but when they are divided into 500 Gm. groups, the average length of gestation is slightly shorter in twins in all of those over 2,000 Gm. (Table II). This suggests that these fetuses would have been greater than the average weight for single fetuses had pregnancy proceeded to term.

*Sex Ratio.*—The infants were of the same sex in 214 pairs of twins and of the opposite sex in 118 (female born first in 59, male born first in 59). Among those who were of the same sex 94 were females and 120 males. A total of 306 infants were of the female sex; 358 were male.\* The ratio of female to male infants in total births according to the United States Bureau of Vital Statistics,<sup>1</sup> is 100:105; in this series of twins the ratio is 100:117.

*Placenta.*—Double placentas were recorded as occurring in 162 pregnancies, single or fused in 156, with no record in 15. In 71.1 per cent of the fused placentas and 58.5 per cent of the double placentas, the twins were of the same sex.

The average ratio between the placenta and the infant birth weight is similar to that generally considered normal for single pregnancies which according to Adair and Thelander<sup>6</sup> averages 1:7.1. The smaller the infant the lower the ratio and this doubtless accounts for the ratio in this series of twins. In the cases where the placenta was double, the average ratio was 1:6.7, where the placenta was single 1:6.5, and in the combined group 1:6.64. Adequate statements as to conditions of the fetal membranes are available only in the recent records. Among 10 of the dichorionic and 5 of the monochorionic single placentas, the infants were of the same sex; in 9 of the dichorionic and 1 of the monochorionic single placentas, they were of opposite sex. It is interesting that of 15 pairs of twins in this group, in only one were both infants female.

*Position.*—Both twins were in a cephalic position in almost half (159) of the total pregnancies. They were both breech in 25, while in 85 the first was cephalic, the second breech and in 33 the first was breech, the second cephalic. In 19, one twin was in a transverse position, scapula, etc., and in 11 the position of one or both was unrecorded. There are almost twice as many second infants in a breech position at the onset of labor as there are first infants (Table III); the great majority of the unusual presentations, especially scapula, are also found among second twins.

TABLE III. POSITION OF TWIN FETUSES AT THE ONSET OF LABOR

POSITION	FIRST TWIN	SECOND TWIN	TOTAL	PER CENT
Cephalic	261	194	455	68.5
Breech	63	114	177	26.6
Other	2	16	18	2.7
No record	6	8	14	2.2
Total	332	332	664	

*Method of Delivery.*—The type of delivery is shown in Table VI. It is interesting to compare these figures with those obtained from a study of all hospital and home deliveries occurring during the same period. Among the 31,131 deliveries in that series natural cephalic deliveries occurred in 66.5 per cent of the cases, among this series of twins in only 29.5 per cent; low or midforceps in 24.4 per cent,

\*The sex of the 4 abortions is included.

TABLE VII. CAUSE OF DEATH IN RELATION TO WEIGHT

CAUSE OF DEATH	FIRST TWIN		SECOND TWIN		TOTAL
	STILLBORN	NEONATAL DEATH	STILLBORN	NEONATAL DEATH	
Over 2,500 Gm.					
No abnormality—fresh		2	1		2
No abnormality—mac- erated					1
Intracranial hemorrhage				3	3
Anoxemia		1			1
Pneumonia				1	1
Malformations	1			1	2 10
1,000 to 2,500 Gm.					
No abnormality—fresh	1	7	2	8	18
No abnormality—mac- erated	2		7		9
Intracranial hemorrhage	1	1		1	3
Anoxemia	2	4	2	2	10
Pneumonia		1		1	2 42
Under 1,000 Gm.*					
No abnormality—fresh	4	8	1	8	21
No abnormality—mac- erated	2		2		4
Ruptured liver		1			1
Anoxemia	1	1	1	3	6
Pneumonia	1		2		3
Malformations	1			1	2 37
No record of weight			2	1	3 3
Total	16	26	20	30	92

\*Includes 4 abortions.

Adair<sup>7</sup> in 1930 reviewed the incidence of malformations in association with the birth of twins in the preceding 25,000 deliveries at the Chicago Lying-in Hospital. The incidence of twin to single pregnancies was about 1:70 with malformations occurring in only 1 per cent of the twin infants. In no instance were both twins of the pair malformed.

*Maternal Complications.*—Some abnormal state was present during pregnancy in 34.0 per cent (113) of the mothers bearing twins (Table VIII). The most common complication was pre-eclamptic toxemia (62), but the incidence of eclampsia was much higher than it was among women with a single fetus. The incidence of

TABLE VIII. MORTALITY IN RELATION TO MATERNAL COMPLICATIONS

	TOTAL MOTHERS WITH COMPLICATIONS	MOTHERS WITH 1 OR MORE DEAD INFANTS OR FETUSES	NUMBER OF FETAL AND NEONATAL DEATHS
Toxemia	62	7	8
Eclampsia	9	1	1
Hypertension	7	2	2
Nephritis	1	1	2
Placenta previa	4	3	6
Syphilis	3	0	0
Hydramnios	5	2	4
Pyelitis	2	0	0
Anemia	13	0	0
Cardiac	4	0	0
Hyperthyroid	2	0	0
Gaucher's disease	1	1	1
Total	113	17	24

infants, 14.1 per cent of twins). Of the infants weighing less than 1,500 Gm., 25 per cent survived. In his group of twins Goecke<sup>7</sup> reports 10.3 per cent of those in this group survived to the tenth day.

Among the 64 pregnancies in which one or both twins died or were stillborn, 50 were of the same sex (21 female, 29 male) and 14 were of the opposite sex. In 26 the placenta was double, in 36 it was single or fused, and in 2 there was no record. Death occurred to one or both twins slightly more frequently (23.0 per cent) when the placenta was single than when it was completely double (16.0 per cent).

*Mortality in Relation to Method of Delivery.*—The mortality among twins in relation to the method of delivery is difficult to compare with mortality in single pregnancies because of the greater incidence of prematurity in the former group, a condition which necessarily increases the number of deaths regardless of the type of delivery. Of greatest significance is the variation in the figures for version and extraction, the mortality among twins (8.6 per cent) delivered by this method being less than one-fourth that of all infants and fetuses delivered (34.5 per cent) in a similar fashion (this figure includes twins) (Table VI). The lower incidence is probably attributable (1) to the fact that when the operation is performed for the delivery of a single infant, it is done only in the presence of severe complications which in themselves greatly endanger the life of the fetus and (2) to the fact that it is a much more difficult technical procedure than when performed on the second twin. In the latter case the uterus is relaxed and one infant has already passed through the birth canal so that the operation itself presents relatively little difficulty.

TABLE VI. MORTALITY IN RELATION TO METHOD OF DELIVERY

METHOD OF DELIVERY	NUMBER OF BIRTHS		STILLBIRTHS AND NEONATAL DEATHS		
	FIRST TWIN	SECOND TWIN	WEIGHT UNDER 1,000 GM.	WEIGHT OVER 1,000 GM.	PER CENT MORTALITY OVER 1,000 GM.
Cephalic					
Natural	137	58	14	18	9.9
Low forceps	87	15	0	4	3.9
Mid or high forceps	14	4	0	1	5.5
Version and extraction	1	115	1	9	8.3
Breech	62	105	14	17	11.6
Cesarean section	22	22	2	1	2.2
No record	9	13	7	4	18.1
Total	664	92	38	54	8.6

*Mortality in Relation to Anatomic State of Infant.*—Over half of the dead infants and fetuses failed to show abnormalities at post-mortem examination (Table VII). Intracranial hemorrhage was present in 6, evidence of interference with umbilical circulation in 17, pneumonia in 6, and malformations in 6. Only 4 of the latter were believed to have died of the malformations.

Malformations are present in a much higher proportion of all twins including those that survive, than of single pregnancies, the incidence among total twins in this series being 2.8 per cent. This lends support to the belief that an abnormal intrauterine environment may in some cases be responsible for the abnormality. In only three instances were similar abnormalities found in both twins. These were 2 infants with umbilical hernias, 2 infants with cavernous hemangiomas of the anterior abdominal wall, one having, in addition, another hemangioma of the leg, and a third pair of infants in both of whom a diagnosis of congenital heart disease was made at two and twelve months, respectively. Among the infants who died, the malformations were all found in one twin of each pair. They were hydrocephalus, anencephalus, cleft palate and harelip, clubhand, mongolism, and congenital heart disease. Among those who survived there were harelip and cleft palate (present twice), hemangioma of lip, umbilical hernia, 6 fingers and toes, hypospadias, and hydrocephalus.



The average length of gestation is 256 days in twin pregnancies, 281 days in all other pregnancies in this hospital.

The combined fetal and neonatal death rate for 660 reportable twin infants is 13.3 per cent; for twin infants over 1,000 Gm. it is 8.4 per cent. The total hospital mortality for reportable births is 4.4 per cent.

The incidence of hypertensive, pre-eclamptic and eclamptic toxemia among twins is more than three times that found in single pregnancies.

Prematurity is the outstanding cause of death in twin infants. Maternal complications are probably not an important factor in producing fetal death.

In this series the second born twin does not appear to have an increased birth hazard.

#### REFERENCES

- (1) United States Department of Commerce. Birth, Stillbirth and Infant Mortality Statistics 1938, United States Printing Office. (2) *Potter, E. L., and Adair, F. L.*: J. A. M. A. 112: 1549, 1939. (3) *Potter, E. L.*: Arch. Path. 25: 607, 1938. (4) *Potter, E. L., and Adair, F. L.*: Fetal and Neonatal Death, 1940, University of Chicago Press. (5) *Daiser, K. W.*: Arch. f. Gynäk. 169: 754, 1939. (6) *Adair, F. L., and Thelander, H.*: AM. J. OBST. & GYNEC. 10: 172, 1925. (7) *Adair, Fred L.*: AM. J. OBST. & GYNEC. 20: 539, 1930. (8) *Guttmacher, A. F.*: Ibid. 38: 277, 1939. (9) *Goecke*: Arch. f. Gynäk. 169: 317, 1939. (10) *Dieckmann, W. J., and Brown, I.*: AM. J. OBST. & GYNEC. 38: 214, 1939. (11) *McChure, H. I.*: Ulster M. J. 6: 284, 1937. (12) *Davis, M. Edward*: Unpublished data. (13) *McIlroy, A. L., and Evans, E. C.*: Med. J. & Record 126: 359, 1927.

## A CLINICOPATHOLOGIC STUDY FROM THIRTY-TWO CASES OF CHORIOEPITHELIOMA

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CHORIOEPITHELIOMA is such a malignant tumor, predisposed to early metastasis, and occurring not infrequently among women of childbearing age, that any data concerning it should be utilized with the view of its early recognition and consequent eradication. Hence the purpose of the present study.

This study, based on 32 cases, includes the patients that had been admitted in the obstetric, gynecologic and medical wards from February, 1937, to November, 1940. The fact that 32 cases of chorioepithelioma whose diagnosis has been established or corroborated by operation, histologic examination, x-ray, or autopsy findings occurred in the short span of three years and nine months, shows that the tumor is indeed far from being rare, at least in the Philippine General Hospital. Perhaps the earlier belief in the rarity of this tumor is not based on reality but on the failure of its recognition.

*Incidence.*—Among the 21,765 obstetric cases admitted from February, 1937, to November, 1940, 32 were cases of chorioepithelioma giving a proportion of 1 case of chorioepithelioma for every 680 obstetric patients. During the same period,

eclampsia, 2.7 per cent, approximates closely that of other reports. Combining his figures with those of several other authors, Guttmacher<sup>8</sup> found an incidence of 2.79 per cent in 1,288 twin pregnancies. Goecke<sup>9</sup> reported 2.3 per cent in 131 cases. The total women in this series with pre-eclamptic, eclamptic, and hypertensive toxemia number 78, an incidence of 23.5 per cent. This is over 3 times the general incidence found by Dieckmann and Brown<sup>10</sup> at the Chicago Lying-in Hospital. It is difficult to compare these figures with those reported by other writers because of the varying criteria used in making a diagnosis of toxemia. However, McClure<sup>11</sup> found an incidence of 40 per cent pre-eclampsia and eclampsia in 165 cases. Guttmacher<sup>8</sup> had 35.3 per cent of late pregnancy toxemia, which was roughly two and one-half times the incidence in all pregnancies at the Johns Hopkins Hospital. Goecke<sup>9</sup> reports a 35 per cent incidence of hydrops, nephropathia, pre-eclampsia and eclampsia in a series of 131 twin pregnancies.

It is interesting that of the 11 fatalities in this group among infants born of mothers with some form of toxemia in only one pregnancy did both twins die. In this instance, one of the infants was malformed, the other died of intracranial hemorrhage following a version and extraction. In the other 9 women, only one twin died; if the toxemia produced direct detrimental effects on the fetuses which resulted in death, as it is commonly believed to do, one would have expected a similar effect on both twins. It suggests that death is coincidental rather than a direct result of the toxemia.

There were 7 mothers with essential hypertension, 2 of whom lost one baby each. In one of these there was a prolapsed cord, in the other polyhydramnios. Of the two mothers with nephritis, one delivered 2 stillborn fetuses, each weighing less than 1,200 Gm. while both of those from the other mother were born alive and survived.

There were 4 cases of placenta previa among the twin pregnancies and in 3 both twins died. All 6 twins weighed less than 1,500 Gm. The incidence of placenta previa does not vary appreciably from that found in association with single pregnancies. Davis<sup>12</sup> states that the total incidence in the Chicago Lying-in Hospital since the opening of the present building in 1931 is 1:102 or practically one per cent. The incidence of 1:83 among twins is probably accidental due to the smaller number of cases. Due to the greater proportionate part of the uterus occupied by the placenta in twin pregnancies one would expect that at least a marginal insertion might be somewhat more frequent.

There were 7 cases (2.1 per cent) of polyhydramnios in the series, one case being included under the pre-eclamptic group, and one under the hypertensive group. The incidence is lower than generally reported. The various estimates of polyhydramnios range from 3.6 per cent (McClure<sup>11</sup>) to 24 per cent (McIlroy<sup>13</sup>). Among the deaths in which polyhydramnios was the only complication both twins were previsible in one case, a third was macerated, and the fourth died of intracranial hemorrhage.

Although the incidence of complications is somewhat higher in twin than in single pregnancies, maternal abnormalities do not in general seem to be responsible for the higher fetal and infant death rates. It is of particular interest that premature detachment of the placenta did not occur in twin pregnancies.

There were no maternal deaths in this series. In a group of 1,163 cases of viable twin pregnancies collected from the recent literature by Guttmacher,<sup>10</sup> there were 23 maternal deaths (2 per cent). Adding our 305 cases of viable twin pregnancies to his series, there would be a combined maternal mortality of 1.5 per cent.

#### SUMMARY

Three hundred and thirty-four multiple pregnancies occurred in 31,131 total deliveries, an incidence of one in 93.4 for twins, and one in 15,514 for triplets.

The average birth weight is 2,391 Gm. for an infant which is one of twins and 3,405 Gm. for other infants born in this hospital.



Fig. 1.—Normal placenta, mole, and chorioepithelioma. Twin pregnancy with one live eight months' fetus and a mole, which developed chorioepithelioma with metastases in vagina, lungs, and brain.



Fig. 2.—Chorioepithelioma of the uterus with metastasis into the right broad ligament.

the relative incidence of chorioepithelioma among the different terminations of pregnancy was as follows:

- 1 chorioepithelioma for every 9.14 cases of mole
- 1 chorioepithelioma for every 474.44 cases of abortion
- 1 chorioepithelioma for every 4,563 cases of labor

The age incidence of chorioepithelioma among this set of cases was between 18 and 49. In a previous study, however, the youngest patient affected was 17 years.

We found that the chorioepithelioma is by far more common in multiparas than in primiparas. Of the 32 cases studied, 21 followed hydatidiform mole, 7 cases after abortion, and 4 cases after full-term labor.

In 3 of the 21 cases following mole, the mole and the chorioepithelioma were coexistent. One of these three was a case of twins where one was a live eight months' fetus with a normal placenta, and the other, a mole with metastatic chorioepithelioma in the vagina, lungs, and brain.

The fact that a normal placenta with its normal fetus may coexist with chorioepithelioma does not support Fleischmann's etiologic theory of chorioepithelioma which is the lack of a lytic substance in the maternal blood which normally prevents the abnormal invasion and proliferation of chorionic cells. For, if the theory were correct, then the coexistence of a normal placenta and chorioepithelioma would not be possible. The evidence seems to point out that the abnormality resides in the chorionic cell itself rather than in the maternal blood.

Of the 32 cases studied, 26 gave a history of uterine bleeding. The remaining 6 gave, respectively, the following complaints: pernicious vomiting, hypogastric pain and abdominal enlargement, headache and numbness of the left half of the body, unconsciousness and headache, vomiting and unconsciousness. In one case the symptoms indicative of brain metastasis occurred three years after an abortion. Twelve of the 32 cases had complications as follows:

Perforation of the uterus by the tumor	8 cases
Intestinal obstruction caused by the growth	1 case
Pneumonia	2 cases
Pulmonary tuberculosis	1 case

Of the 8 cases of uterine perforation, 2 had intra-abdominal hemorrhage, and 2 had pelvic abscess.

Twenty-one of the 32 cases showed metastasis in different organs at the same time as revealed by laparotomy and x-ray of the lungs or by autopsy. The relative frequency of the organs affected was as follows:

Lungs	18 cases
Vagina	5 cases
Brain	4 cases
Broad ligament	4 cases
Intestines	3 cases
Spleen	2 cases
Kidney	2 cases
Liver	1 case

*Diagnosis.*—In 25 of the 32 cases, there were three factors which were consistently found and which we have come to believe, when present, constitute a positive clinical method of diagnosis. These data are: (1) History of having passed mole or of having aborted; (2) uterine bleeding; and (3) the finding on abdominopelvic examination of an enlarged soft uterus as if it were pregnant. For easier remembrance, we have labeled these data as *H. B. Es.* in which *H* stands for history of a last pregnancy ending in mole expulsion, or abortion or even full-term delivery; *B* stands for uterine bleeding; and *Es* stands for the enlargement and softening of the uterus.

The uterine bleeding, which varied from slight to profuse, and was either continuous or intermittent, appeared any time within six months after the termination of

The reasons for objecting to the performance of the diagnostic curettage in the presence of the data *H. B. Es.* are as follow :

1. If the result is positive, it merely confirms the diagnosis already made by the data *H. B. Es.*, and nothing has been gained.

2. If the result is negative, it will not alter the positive diagnosis arrived at through the data *H. B. Es.* nor the decision for radical treatment. In many of our cases, the tumor was found to be in the muscular wall far beyond the reach of the curette so that in these cases, uterine scrapings would have invariably given a negative finding.



Fig. 4.—Microscopic section of a perforated chorioepithelioma. Both Langhans' cells and syncytial cells are seen, with a preponderance of the former.

3. The use of the curette may give rise to infection in a uterus that, because of its softness, has become susceptible to germ growth.

4. The curette may perforate the uterus in cases where the growth has extended throughout the thickness of the uterine wall and thus increase the danger of a radical operation.

5. It may incite the rapid flaring up of metastasis.

6. At best, it is a misuse of time and energy unnecessarily, if not dangerously, delaying the performance of a radical operation which should be done as early as possible.

the last pregnancy. The uterine bleeding should not be preceded by amenorrhea which may indicate pregnancy. The size and contour of the uterus depended on the size of the growth within and on the presence or absence of extension of the tumor in the surrounding vicinity of the uterus. In one case where the chorioepithelioma was of the size of a button 1.5 cm. in diameter, the uterus had the size of a one month's pregnancy. In another case, the size of the uterus was that of a four and one-half months' pregnancy.

The uterus affected with chorioepithelioma is soft when relaxed, but sometimes it contracts; then it becomes as hard as any contracting pregnant uterus.

An intelligent interpretation of the data as represented by *H. B. Es.* will rule out extrauterine pregnancy. Either case, however, calls for laparotomy. Uterine pregnancy with symptoms of threatened abortion should be eliminated.



Fig. 3.—Microscopic section of the tumor of Fig. 2.

The senior author of this paper has done 13 hysterectomies on the basis only of the data represented by *H. B. Es.*, very often on the hour of admission to the hospital, and it was found that the positive diagnosis of chorioepithelioma in these cases was invariably supported by the gross and histologic examinations of the tumor in the uterus. Except in very doubtful cases where the uterus is not appreciably enlarged, we not only do not employ but also strongly object to the performance of the so-called "diagnostic curettage," a measure which most authors, if not all, believe to be the only way of making a positive diagnosis. We make diagnostic curettage only when the uterus is not enlarged and the diagnosis is doubtful. And we follow the verdict of the Friedman test only in doubtful cases when all the data as represented by *H. B. Es.* are not present.

existence in a case of twins, of a normal placenta with its live fetus and a hydatidiform mole and metastatic chorioepithelioma.

7. The removal of the primary chorioepithelioma does not bring about the reabsorption of its metastasis.

8. A clinical method of diagnosis of chorioepithelioma is presented.

9. Friedman's test in chorioepithelioma is evaluated.

10. Negative x-ray findings in lungs for chorioepithelioma in the presence of lung symptoms do not necessarily indicate absence of metastasis unless proved otherwise or unless the negative findings persist four to five weeks after the first examination.

11. Surgical removal of the tumor in accessible places and early x-ray treatment of the lungs, should they be affected by metastasis, give the highest percentage of recovery.

We wish to acknowledge our indebtedness to Dr. Wilfrido de Leon who made the microscopic examinations of the specimens.

#### REFERENCES

- (1) *Acosta-Sison, H., and Galang, J.*: J. Philippine M. A. 17: 457, 1937. (2) *Fleischman*: From Mathieu and Robertson, Surg. Gynec. & Obst. 69: 158, 1939. (3) *Dickson, J. C.*: U. S. Nav., M. Bull. 33: 358, 1935. (4) *Mathieu, A., and Robertson, T. D.*: Surg. Gynec. & Obst. 69: 158, 1939.

### A COMPARATIVE STUDY OF PREGNANCY IN THE WHITE AND COLORED RACES\*

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A COMPARATIVE study of pregnancy in a series of 1,000 indigent white women with 1,000 consecutive pregnancies in colored women, all residing in Mecklenburg County, North Carolina, is here presented. By way of introduction, the notoriously high maternal death rate in the southern United States has primarily been ascribed to social and economic causes, a major factor being the large percentage of the child-bearing populace that are members of the colored race. The maternal mortality rate among negroes throughout the country has always been higher than among whites and has failed to show the substantial reduction that has applied in the white mortality during the past few years. In the United States the rate for negroes in 1938 was 8.6 per 1,000 births as compared with 9.3 in 1934, a reduction of 8 per cent. The mortality rate for white mothers in 1938 was 3.8 per 1,000 births as compared with 5.4 in 1934, a reduction of 30 per cent. In other words the maternal mortality rate among negroes throughout the entire United States in 1938 was more than double the white mortality rate. North Carolina was quite comparable with the United States as a whole in this respect, the

\*Presented at a meeting of the North Carolina Medical Society, Pinehurst, May 19 to 21, 1941.

*Friedman Test.*—We follow the verdict of the Friedman test in cases where the data of the *H. B. Es.* are not present, also in the follow-up of cases after treatment.

*Treatment.*—Four patients with uterine chorioepithelioma were treated by x-ray. Only one patient was saved, and this was a very early case. The rest died. Nineteen cases were subjected to radical operation of hysterectomy in addition to salpingectomy, oophorectomy, and partial excision of the broad ligament in cases where these structures were affected by metastasis. Of these 19 cases, 6 had lung metastasis which was untreated by x-ray. These 6 patients died later from the extension of the lung metastasis. The death of these patients shows that the removal of the primary tumor does not bring about the recession of metastatic growth in other organs, as has been affirmed in obstetric literature.

One case of early lung metastasis was treated by x-ray. And this is the only case of lung metastasis in our series that recovered. This particular case was one wherein the chorioepithelioma had perforated the uterus with about 200 c.c. of blood in the peritoneal cavity and a thin metastatic growth over the rectum. The intestinal metastasis was treated by x-ray. It is now seven months since the operation and x-ray treatment, and the patient continues to be well, with a negative Friedman test.

Three of the patients with uterine chorioepithelioma had vaginal metastasis. These were treated by surgical enucleation of the vaginal tumor in addition to hysterectomy. One of the patients operated upon died of peritonitis due to the perforation of the uterus by the chorioepithelioma.

Of the 19 patients operated upon, 12 recovered.

One patient (the case cited above) was subjected to intramuscular injection of serum from a pregnant woman for the purpose of giving her the benefit of the lytic substance postulated by Dickson, Mathieu, and others as existing among pregnant and puerperal women who do not develop chorioepithelioma. However, since this patient was also treated surgically and by x-ray, we cannot attribute her cure to the intramuscular injection of the puerperal blood serum.

The result of this study points to early hysterectomy and early x-ray exposures of the lung metastasis as the surest form of treatment. X-ray treatment for uterine chorioepithelioma may be considered only in very early cases and where a contraindication exists for laparotomy; and patients receiving such form of treatment should be carefully followed up for the return of the symptoms of bleeding or for the positive Friedman test. Moderately advanced cases do not yield to x-ray treatment.

#### SUMMARY AND CONCLUSIONS

1. This study is based upon 32 cases of chorioepithelioma.
2. Chorioepithelioma may occur in individuals from the age of 17 to 49 years.
3. Chorioepithelioma is more common in multigravidas than in primigravidas.
4. It may occur after full-term labor, but it is more common after abortion and especially after mole expulsion.
5. Symptoms indicative of chorioepithelioma may appear from the day after the termination of pregnancy to three years thereafter.
6. The belief that the chorionic cell is abnormal per se, and that in normal women it does not develop into chorioepithelioma because of the supposed presence of a lytic substance, is not supported by the co-



aid in answering some of the problems of the high maternal mortality in the southern states. Is the southern rate high because of the negro or is it because of the social and economic circumstances under which she lives and breeds. In short, is race per se really a factor in maternal mortality? (Table I.)

TABLE IV. GRAVIDITY

	1,000 COLORED	1,000 WHITE
Primipara	30%	22%
Multipara	70%	78%

TABLE V. HEMORRHAGE

	1,000 COLORED	1,000 WHITE
Post partum	2.1%	2.3%
Placenta previa	0.5%	0.3%
Premature separation of placenta	0.5%	0.6%
Total	3.1%	3.2%

*Comment.*—No racial difference is noted in the study of hemorrhages complicating pregnancy.

TABLE VI. LABOR

	1,000 COLORED	1,000 WHITE
Precipitate delivery	27.9%	14.2%
Labor over 24 hours	6.4%	6.6%
Labor over 48 hours	1.1%	1.5%

*Comment.*—Aside from a higher incidence of precipitate delivery in the negro (naturally high in any home delivery service), there is no striking racial difference in the duration of labor. The incidence of prolonged labor is quite similar in the two races.

TABLE VII. OPERATIVE INCIDENCE

	1,000 COLORED	1,000 WHITE
Low forceps	1.2%	3.7%
Midforceps	0.4%	0.7%
Version	0.4%	0.1%
Breech extraction	0.2%	0.6%
Curettage	0.0%	0.2%
Hysterotomy	0.6%	0.3%
Cesarean section	0.9%	1.0%
Total	3.7%	6.6%

*Comment.*—The operative incidence in the white race of 6.6 per cent is higher than the incidence in the negro of 3.7 per cent, chiefly because of a greater use of low forceps in the white patients (37 cases in the white as compared to 12 in the 1,000 negroes). Elimination of this variation leaves a similar incidence of major obstetric procedures in the two races. Even the operation of cesarean section shows no racial difference: 9 cases in 1,000 whites and 10 cases in 1,000 negroes.

From the study of duration of labor and operative incidence, no clinical pelvic racial variation occurs that is not well compensated for by other factors. The end result of delivery confirms this observation. While a contracted pelvis is generally accepted as more frequent in the colored race, nature apparently produces a termination of pregnancy that is as effective as in the white patient.

total maternity death rate in 1938 being 5.6 per 1,000 live births, divided as follows: white, 4.4; negro, 8.3.

The comparative study of 2,000 consecutive pregnancies here presented was undertaken as an effort to ascertain if the colored patient is a greater obstetric hazard than the white patient living under similar social and economic circumstances. The private white patient naturally utterly fails as fair comparative data. The 1,000 consecutive white pregnant women herein reported were all indigent patients living in the poorer sections of the city or on tenant farms, and their dietary, economic, and environmental circumstances are comparable to the negro. Such comparisons as are here presented, expanded on a wide scale might

TABLE I. COMPARATIVE MORTALITY RATE BY RACE, FROM THE NORTH CAROLINA BUREAU OF VITAL STATISTICS

	WHITE	COLORED
1930	6.7/1,000	12.2/1,000
1932	5.8	10.3
1934	6.7	9.7
1936	5.9	9.6
1938	4.5	8.4
1939	4.0	6.7
Total deaths 1930—640		
Total deaths 1939—394		

TABLE II. INCIDENCE OF PRENATAL CARE

	1,000 COLORED	1,000 WHITE
None	2.1%	10.8%
Inadequate (4 visits or less)	29.0%	33.0%
Good	68.9%	56.2%

*Comment.*—The Charlotte Maternity Clinic offers a prenatal service for indigent patients by means of a large central city clinic and five subclinics in rural sections of the county. This means that prenatal care is readily accessible to every resident of the city and county. In the early years of this program, it was thought that the negroes would be too indifferent and ignorant to avail themselves of this service. Such has not been the case; rather the white patient has proved to be less responsive and more immune to maternal welfare education than the negro. One hundred and eight white patients in this series had no prenatal care as compared to only 21 negroes. Six hundred and eighty-nine negroes had excellent prenatal care as compared to 562 whites. The illiterate white class is in many respects a greater social problem than the negro. Apparently they are less receptive to organized and competent maternal care.

TABLE III. AGE GROUP

	1,000 COLORED	1,000 WHITE
10-19 years	35.2%	20.5%
20-29 years	50.0%	51.0%
30-39 years	14.0%	25.0%
40 plus years	0.8%	4.5%

*Comment.*—This analysis conforms with the accepted knowledge as to the early reproductivity of the negro and likewise her declining fertility in the fourth and fifth decades of life.

TABLE XII. MATERNAL MORTALITY

	1,000 COLORED	1,000 WHITE
Premature separation of placenta	0	1
Pneumonia	0	1
Post-partum hemorrhage	1	1
Ruptured uterus	1	0
Spinal anesthesia	1	0
Eclampsia	1	1
Acute pre-eclampsia	0	1
Chr. hypertensive disease	1	0
Post-partum infection and toxemia	0	1
Total	5	6

*Comment.*—Toxemia of pregnancy was a major factor in 5 of the 6 white maternal deaths and in 3 of the 5 colored maternal deaths.

TABLE XIII. ASSIGNMENT OF MAJOR RESPONSIBILITY FOR MATERNAL DEATHS

	COLORED	WHITE
Unavoidable	0	2
Physician	2	2
Patient	3	2

*Comment.*—From the standpoint of assignment of primary responsibility the maternal deaths occurring in this series of 2,000 indigent patients may be divided into three arbitrary groups: those due to the patient, those due to the physician, and those nonpreventable.

utilize such services. Often a failure at intelligent cooperation, a condition not unusual in this class of individual, directly results in a maternal death.

In discussing maternal deaths due to errors in medical judgment, the very nature of a free clinic service presents limitation of professional interest and a lower professional standard than that represented in the relationship of qualified private physicians to paying patients. In addition to inadequate medical supervision, the problem of a changing and inexperienced medical personnel, the inevitable price of a teaching service, can unfortunately be involved as a factor in maternal mortality.

Third and last are the group of nonpreventable maternal deaths. The irreducible minimum has yet to be defined but the nature of pregnancy itself results in hazards in any race that are occasionally fatal.

#### CONCLUSIONS

1. The incidence of toxemia of pregnancy and of syphilis is higher in the colored than in the white race.

2. No striking racial differences were noted in the incidence of hemorrhage, infections, operative deliveries or other contributory causes of infant and maternal mortality.

3. Toxemia and chronic vascular pathology, together constitute the outstanding pathologic factor in maternal mortality occurring in the indigent, being the major or contributing cause in the death of 8 of the 11 maternal deaths in this series of 2,000 patients.

Even in a fairly concentrated area of population where adequate maternal and hospitalization facilities are provided, the ignorance and low mentality of the indigent patient frequently result in a failure to

TABLE VIII. TOXEMIA OF PREGNANCY

	1,000 COLORED	1,000 WHITE
Pre-eclampsia	11.40	6.90
Eclampsia	1.5	0.5
Hypertensive vascular disease	5.8	7.9
Total	18.7%	15.3%

*Comment.*—The incidence of eclamptogenic toxemia of pregnancy appears higher in the negro than in the white cases studied. This is the most positive finding in this study and might be interpreted as a contributing cause of the higher negro maternal mortality reported in vital statistics.

TABLE IX. INDUCTION OF LABOR

	1,000 COLORED	1,000 WHITE
Bag	0	0
Rupture of membranes	1.7%	2.8%
Bougie	0.1%	0.1%

TABLE X. COMPLICATIONS

	1,000 COLORED	1,000 WHITE
Organic heart disease	0.6%	0.6%
Tuberculosis	0.5%	0.3%
Fetal abnormalities	0.5%	1.4%
Syphilis	23.7%	5.9%
Puerperal infection	0.8%	1.9%

*Comment.*—The high incidence of syphilis in the colored patients (237 cases in this series of 1,000 deliveries) while probably not a factor in maternal mortality requires comment as a contributing cause of maternal morbidity and fetal mortality. Likewise the higher incidence of fetal abnormalities in the white patients (1.4 per cent white, 0.5 per cent colored) is in conformity with published observations on this subject.

No other striking differences in the incidence of medical complications were noted.

An apparently higher incidence of infection in the white patients is not worthy of evaluation, as the delivery of the majority of these patients in the home did not permit an accurate study of morbidity.

TABLE XI. INFANT MORTALITY

	1,000 COLORED	1,000 WHITE
Miscarriage	2.4%	3.4%
Stillbirths	4.0%	3.3%
Neonatal deaths	4.2%	3.0%
Total infant loss	10.6%	9.7%

*Comment.*—No striking racial difference appears in the incidence of stillbirths. The incidence of miscarriage is near similar. The higher incidence of neonatal deaths in the colored (4.2 per cent) as compared to the white (3.0 per cent) is probably related to the higher incidence of syphilis in the former.

use. A simple, cheap and practical method for the production and administration of plasma has been developed. It may be easily installed in any hospital, however small.

The equipment necessary for the production of plasma follows:

1. A donor valve set.
2. A vacuum bottle containing 70 c.c. of  $2\frac{1}{2}$  per cent sodium citrate in physiologic saline.
3. A vacuum bottle containing 250 c.c. of physiologic saline.
4. An aspirating needle.
5. An icebox.
6. A record system.

The problem of procuring donors was readily solved. It is routine, on the admission of any patient with a history of bleeding, to send for donors who are promptly typed and crossmatched, in order to be prepared for transfusion, if it should become necessary. Now, instead of typing prospective donors until one with a suitable cross match is found, blood for the plasma bank is drawn from each one of them. They are told that if their blood is not used for their relative or friend, it will be used for some other patient in need of a transfusion. Another small but valuable source of plasma is phlebotomy. When a plasma bank is established it becomes self-supporting, as recipients of plasma are told that a relative or friend must donate blood to make up for what has been given to them. We have not as yet failed of repayment. In fact, we often obtain a double return.

#### PROCEDURE FOR PRODUCTION OF PLASMA

A complete physical examination is performed on the donor who signs an agreement to donate his blood to the plasma bank. Under operating room aseptic technique, slightly over 500 c.c. of blood is drawn, using the donor valve set, into a vacuum bottle containing 70 c.c. of  $2\frac{1}{2}$  per cent sodium citrate in physiologic saline solution. The blood remaining in the tubing is drained into a test tube, which is sent to the laboratory for typing and serology. The typing of the blood is unnecessary, but is done for our own studies and for the donor's information. The citrated blood is then placed in the icebox at  $4^{\circ}$  C.

The blood is kept in the icebox for from five to seven days. It has been shown that sedimentation of the cells is greatest at this time, while hemolysis is minimal. The citrated blood has now separated into two layers. The lower layer is composed of cells; the supernatant fluid is the plasma which may now be drawn off. A greater yield of plasma may be obtained by centrifugation, but this entails the addition of costly apparatus and a considerable increase in the detail of technical procedure. Furthermore the difference in the yield of plasma by centrifugation and sedimentation is but 30 to 50 c.c. Largely because we wished to establish a simple as well as an inexpensive technique, sedimentation appeared to be a satisfactory way to obtain plasma. This we have found to be so.

The aspiration of plasma is also done under aseptic technique. By means of the same donor valve set used in drawing blood, the supernatant plasma is aspirated into a vacuum bottle containing 250 c.c. of physiologic saline solution, substituting a long aspiration needle for the venipuncture needle (Fig. 1). While undiluted plasma may be

4. The negro patient is often more appreciative, cooperative, and receptive to an organized maternal welfare program than the indigent southern white.

5. The high maternal mortality throughout the southern United States is not primarily due to the colored race but due to the social and economic circumstances confronting a large percentage of the populace, including the negro. Race per se is not a major contributing factor in maternal mortality.

Indebtedness and appreciation are hereby expressed to Dr. Everett Sawyer for his aid in collecting data summarized in this paper.

1509 ELIZABETH AVENUE

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## PLASMA IN OBSTETRICS\*

### WITH A SIMPLE METHOD FOR ITS PRODUCTION

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THE efficacy of plasma in the treatment of hemorrhage and shock, whatever its nature, is now well known.<sup>1, 2</sup> Plasma is peculiarly adapted for obstetric needs. Obstetric hemorrhage and shock require immediate and adequate replacement of blood volume. Until recently, this meant transfusion of whole blood procured either from actual donors or from a blood bank. In the case of donors, actual time trials have shown that an average of at least two hours will elapse from the time donors are called until blood is available. Even if the donor is present in the hospital, necessary preparations require forty-five minutes before transfusion may be given. In the case of blood banks further time trials have shown that a minimum of thirty minutes is required before blood is available. Furthermore, blood banks are not unfailing sources of supply. Even the largest bank may find it impossible to supply a call for one of the rarer blood types or be unable to furnish blood in the quantity needed. On the other hand, plasma is immediately available. There is no need for typing or crossmatching. Plasma may be pouring into the patient's veins one minute after the need becomes apparent.

Convinced that plasma should play a prominent role in the control of the important maternal mortality hemorrhage factor, a plasma bank was organized in November, 1940, in the Department of Obstetrics and Gynecology of St. Catherine's Hospital under the direction of Dr. Charles A. Gordon. The experience of the Blood Transfusion Association of New York<sup>3</sup> in collecting blood for plasma had shown that the closed vacuum system of collecting blood and drawing plasma was an ideal method, because of ease of technique and preservation of sterility. The results of our use of plasma in the treatment of obstetric hemorrhage and shock have been so striking that we now feel that no lying-in institution is properly equipped unless plasma is available for immediate

\*Read, in part, at a meeting of the Obstetric Conference of the Committee on Maternal Welfare of the Medical Society for the County of Kings, March 25, 1941.

## CASE REPORT

CASE 1.—A. M., aged 28 years, para 0, gravida i, expected date of confinement June 9, had a normal antenatal course. She entered the hospital May 31 in active labor. Following a twelve-hour labor, the patient was delivered by low forceps under gas oxygen ether anesthesia of a 6-pound 8-ounce living female in good condition. Placenta was delivered intact ten minutes later; blood loss was 200 c.c. One and one-half hours following delivery, patient suddenly had a profuse hemorrhage of 750 c.c. and went into profound shock. The uterus was massaged manually and ergotrate administered intravenously. Five hundred cubic centimeters of 50 per cent plasma in saline were given immediately. After twenty minutes the condition of the patient was improved and one hour later, another 500 c.c. of plasma solution were given. Patient's condition became normal and signs of shock disappeared. Post-partum course was uneventful thereafter, except for an anemia, for which she received a transfusion of 500 c.c. of citrated blood on the third post-partum day.



Fig. 2.—Administration of plasma through steel mesh filter.

CASE 2.—A. S., aged 26 years, para 0, gravida i, expected date of confinement March 7, had a normal antenatal course, and entered the hospital March 14 in active labor. Examination disclosed a frank breech presentation in the L.S.P. position. Pains were desultory and progress slow. The fetal heart disappeared after twenty-six hours of labor. After fifty-four hours of labor, the cervix was fully dilated, a Bandl's contraction ring was present and the mother was in poor condition. Under gas oxygen ether anesthesia, the anterior leg was delivered by fracturing the femur. The posterior leg was delivered by means of a Braun's hook. Because of the contraction ring, the head could only be delivered by means of a cephalotribe. Following delivery, the patient was in deep shock. Five hundred cubic centimeters of 50 per cent plasma in saline were given with immediate improvement. The post-partum course was uneventful, except for a slight rise in temperature the first three days.

CASE 3.—R. P., aged 25 years, para 0, gravida i, expected date of confinement April 13, had a normal antenatal course, and was admitted to the hospital April

used, the addition of saline solution inhibits precipitation of fibrin, which is more likely to occur in the undiluted plasma. Scrupulous care must be taken not to aspirate any of the cells and, when near the bottom of the plasma layer, the rate of flow should be carefully controlled by the valve. This precaution necessitates leaving a small layer of plasma, usually about three-sixteenths of an inch in depth. Nevertheless, the average yield of plasma from 520 c.c. of citrated blood is about 250 c.c. When the aspiration is completed, the plasma remaining in the tubing is collected and cultured. No antiseptic is used, though many have advised the addition of 5 c.c. of 1 per cent merthiolate solution. We feel that this added step in the procedure, because of the closed system and aseptic technique, is unnecessary. All our cultures have remained sterile.

It should be said that we have not found it necessary to pool plasma. Pooling is done to avoid a high agglutinin titer. However, there is considerable evidence to show that the presence of a high agglutinin titer is harmless.<sup>4</sup> Since this procedure entails added steps in the production

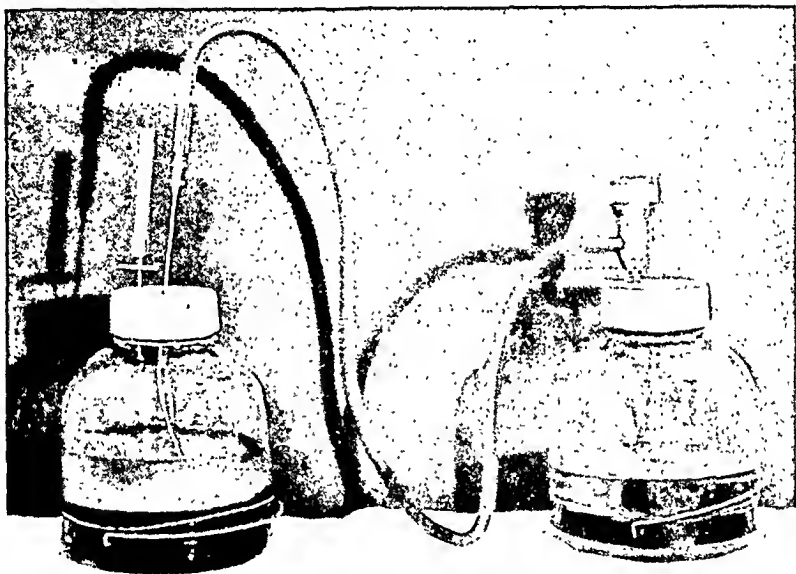


Fig. 1.—Aspiration of plasma.

of plasma, with a greater likelihood of contamination, we have omitted it from our technique. We have given close to 100 plasma transfusions and have had no reactions, though we have made no effort to give plasma of the same type as the recipient.

Plasma is ready for use as soon as the culture is reported negative. No special facilities are required for its storage. It may be kept in a closet, on a shelf, utility room, or any available place. It need not be stored in an icebox. As far as is known, plasma may be safely used after long periods of time.

Plasma is administered in exactly the same manner as a venoclysis, with the exception that the plasma is passed through a steel mesh filter to keep out any precipitate that may have formed (Fig. 2). Sterile recipient sets which contain the tubing, needles, and steel filter necessary for the administration of plasma are kept available in the delivery room. The patient in shock may be receiving plasma one minute after the order is given for its use.



## CONCLUSIONS

1. Plasma is an important addition to our obstetric armamentarium.
2. Plasma may be easily and cheaply obtained.
3. Because of its easy production and low cost, no hospital should be willing to accept obstetric patients unless plasma is available.

I wish to acknowledge the interest and help of Dr. Charles A. Gordon in the preparation of this manuscript.

## REFERENCES

- (1) *Strumia, M. M., Wagner, J. A., and Monaghagh, J. F.*: J. A. M. A. 114: 1137, 1940. (2) *Elliot, J., Tatum, W. L., and Busby, G. F.*: Military Surgeon 88: 118, 1941. (3) Report of the Blood Transfusion Association, New York, 1941, Blood Transfusion Association. (4) *Elliot, J.*: Quoted from the Report of the Blood Transfusion Association, p. 82, January, 1941.

868 PROSPECT PLACE

## ADENOMYOSIS INTERNA UTERI AS A CAUSE OF UNCONTROLLABLE ATONY AND HEMORRHAGE FOLLOWING CESAREAN SECTION FOR SACCULATION PREGNANCY. HYSTERECTOMY\*

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**A**DENOMYOSIS of the uterus is a well-recognized cause of pain and irregular bleeding, and is often associated with impaired fertility. In the event of pregnancy it may lead to abortion, premature labor, or dystocia. Its relation to post-partum atony and hemorrhage has received scant notice in the literature, except for certain accidents due to endometriosis of operative or cesarean scars. In a previously unoperated primigravida, adenomyosis leading to spontaneous rupture of the uterus at the onset of labor was reported in 1937 from the Bellevue service by Melvin Stone.<sup>1</sup> He referred to a similar case described by R. Richardson in 1919. Two others are collected by Batizfalvy;<sup>2</sup> and he cites a report in 1927 by Schweitzer,<sup>3</sup> who was forced to amputate the uterus for atony following cesarean section and found it honeycombed with endometriosis. Hysterectomy for atony and hemorrhage following *normal* delivery was performed by Szenes<sup>4</sup> who reported (1928) similar findings. The paucity of such reports may be due to the fact that pathologic study is available only in the rare cases coming to hysterectomy or to autopsy.

## CASE REPORT

Mrs. M. A. (No. 62810) was first seen March 5, 1936, in the second month of her first pregnancy at 30 years of age. Four years previously she had undergone an appendectomy, resection of cystic left ovary, and round ligament suspension by the Coffey technique. It should be emphasized that ventral fixation was *not*

\*Read at a meeting of the New York Obstetrical Society, May 13, 1941.

17 in active labor. Following a thirty-hour labor, patient delivered spontaneously a living female child, weighing  $5\frac{1}{2}$  pounds. One half hour after delivery with the placenta still undelivered, patient lost about 600 c.c. of blood and went into deep shock. Five hundred cubic centimeters of 50 per cent plasma in saline were given immediately, followed by another 500 c.c. of plasma solution, with marked improvement in the patient. Patient was then given a general anesthesia and the placenta removed manually with ease. There was no further bleeding following this. Subsequent post-partum course was uneventful.

CASE 4.—M. S., aged 34 years, para 0, gravida i, expected date of confinement December 21, was admitted to the hospital January 3, because of a pre-eclamptic toxemia. Patient was placed on routine toxemia therapy, and three days after admission went into labor. After a twelve-hour labor, cervix was fully dilated, and the head was on the perineum. Blood pressure at this time was 168/100. Patient was placed on the delivery table, following which, she had a convulsive seizure lasting three minutes. Low forceps were immediately applied without anesthesia and a living female child weighing  $7\frac{1}{2}$  pounds was delivered from the L.O.A. position. The placenta delivered twelve minutes later. Immediately thereafter patient had another convulsion lasting three minutes, followed by a profuse hemorrhage of 1,500 c.c. with resultant profound shock. Plasma therapy was quickly instituted and 1,000 c.c. administered. There was an immediate and marked improvement in the patient's condition. Post-partum course was subsequently normal except for an anemia, for which transfusions of 500 c.c. of citrated blood were given on the second and seventh post-partum days. There were no further convulsions and the blood pressure on her discharge, twelve days post partum, was normal.

CASE 5.—M. M., aged 34 years, para iii, gravida iv, was admitted February 9 with a history of the last menstrual period being December 7, and of profuse vaginal bleeding accompanied by abdominal cramps for the past twenty-four hours. Patient was admitted in deep shock. Two thousand cubic centimeters of 50 per cent plasma in saline were given in the course of three hours with marked improvement in the patient. Patient was taken to the operating room and under gas oxygen ether anesthesia, a large piece of placental tissue was removed. Post-operative course was uneventful and the patient discharged on the seventh post-operative day.

CASE 6.—M. R., aged 29 years, para i, gravida ii, expected date of confinement February 14, was admitted January 23, for an elective cesarean section. She had a cesarean section performed in 1938 because of a deformed pelvis, secondary to an attack of acute anterior poliomyelitis. On January 28, an elective two flap lower segment cesarean section with transverse incision was performed under local infiltration of 1 per cent procaine. Following delivery of the baby, patient lost about 600 c.c. of blood and evidenced signs of shock. One thousand cubic centimeters of plasma solution were immediately given and patient's condition became markedly improved. Postoperative course was normal except for an anemia for which she received a transfusion of 500 c.c. of citrated blood on the third post-partum day. She was discharged on the fifteenth post-partum day.

As stated above, we have seen no reaction follow the use of plasma. This coincides with the greater experience of Elliot<sup>2</sup> and Strumia.<sup>1</sup> Any reaction to plasma that has been reported may be traced to pyrogens. Scrupulous and painstaking washing of tubing, donor valve and filter is of the utmost importance. A detailed technique for this procedure has been satisfactorily worked out.

The actual cost of setting up the plasma bank, including the cost of all the apparatus needed, exclusive of the icebox, was less than twenty-five dollars. The actual cost of producing 500 c.c. of 50 per cent plasma in saline solution is less than two dollars.

secondary anemia was sufficiently improved to permit discharge on the twenty-fifth post-partum day. The patient remains in normal health up to the present time, except for a susceptibility to trichomonas vaginitis readily controlled by estrogenic therapy.



Fig. 1.—Adenomyosis interna uteri. Papillary and cystic hypertrophy of glandular elements of endometrioid islets in myometrium.

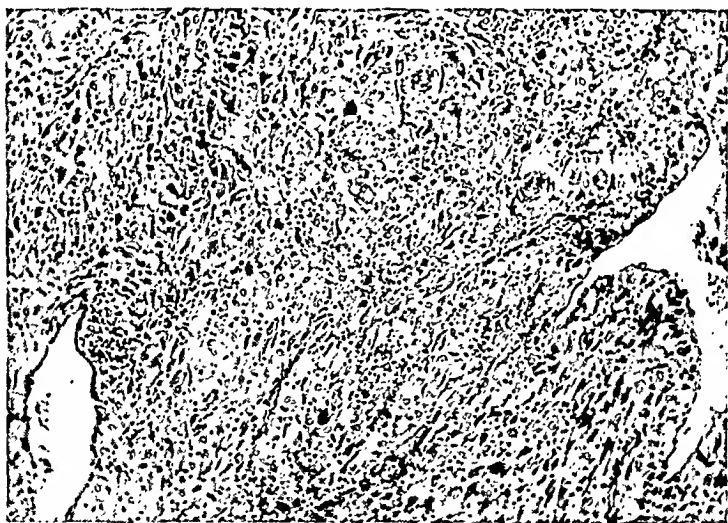


Fig. 2.—Adenomyosis interna uteri. Marked decidual reaction in stroma of endometrioid foci, causing dissociation of fibers of myometrium.

*Pathologic Report by Dr. Motyloff.*—Membranes, cord, and placenta were complete and grossly normal in both pregnancies. The hysterectomy specimen included congested edematous fragments of the tubes but no recognizable ovarian tissue. The uterus measured 18 by 16 by 12 cm., and a cuff of cervix 5 cm. wide and 2 cm. long was attached anteriorly. The anterior surface presented two pockets, on right and left sides, resulting from the Coffey operation. The freshly sutured cesarean incision ran from the amputated border 8 cm. upward parallel and slightly to the right of the midline. The uterus was opened through its posterior wall to permit inspection of this incision. The area near it was occupied by a scar, apparently the remnants of the previous section. The lining was rough, the actual site of the placenta could not be determined, and there was a small amount of clotted blood in the cavity.

done. Menses began at 16, cycle was thirty to thirty-five days, duration and amount average, with mild suprapubic pain for one week before the periods. The general physical examination, blood pressure, and urinalyses were normal, and nothing unusual was noted about the pregnant uterus or cervix.

After a normal pregnancy, labor began spontaneously at forty weeks and remained very active throughout a trial of thirty hours. Examination under anesthesia revealed the cervix extremely high posterior, difficult to reach, very long and tough, and dilated 1.5 cm. The baby lay in R.O.P. with the unengaged head distending the anterior wall of the lower uterine segment far removed from the cervix. The pelvis was entirely ample and the diagonal conjugate was not reached at 13 cm. Under the diagnosis of anterior sacculation pregnancy,<sup>5</sup> cesarean section was performed because of the failure of a thirty-hour trial labor to produce cervical dilatation or engagement of the head.

A living 7 pound 13 ounce (3,544 Gm.) female infant, which survives, was delivered on Oct. 13, 1936, by low flap cesarean section. The skin incision avoided the previous laparotomy scar and care was taken not to disturb the plicated round ligaments, which were spread out over the anterior uterine wall producing several peritoneal folds. The Coffey suspension had *not* resulted in any adhesion to the parietes, the resected left ovary was so thinned out as to be unrecognizable, and the tube spread over the left uterine border. The right adnexa lay free in the lumbar gutter. The lower uterine segment was incised longitudinally and closed in layers with chromic catgut sutures. It is to be noted that the uterus behaved normally through labor and at cesarean, contracting well with the aid of pituitrin 0.5 c.c. intravenously after delivery of the baby, and one ampoule each of pituitrin and ernutin after removal of the secundines. The patient was afebrile on and after the fifth day and was discharged on the sixteenth day, when the cervix was still too high to palpate vaginally.

At follow-up examination one month post partum, the cervix had descended to normal position and the corpus was anterior and mobile. Menses now occurred at irregular thirty-five- to forty-two-day intervals, their prolonged duration and associated cramps being attributed to a stenosis of the upper cervical canal. Although contraceptives were employed only six months, another twelve months elapsed before conception occurred.

Examination in the eighth week of the second pregnancy revealed decreased uterine mobility, and a high posterior cervix with mild chronic inflammation. Pregnancy was again uneventful and elective cesarean section was done February 11, 1939, at forty weeks by the same method. An 8 pound 9 ounce (3,884 Gm.) female infant was delivered and now survives. This time the uterus looked healthy, and the round ligaments and adnexa as at the former cesarean; and the lower uterine segment was covered by numerous reduplications of peritoneum, permitting ample upper and lower flaps to be developed. The lower segment was again incised longitudinally, and after removal of infant and complete membranes and placenta it was again closed in layers with chromic catgut. The usual intravenous pituitrin after delivery of the baby and ergotrate after removal of the secundines were given and the initial blood loss was about average during the closure of uterus and peritoneal flaps. Before the abdominal closure was begun, however, the anesthetist reported a rapidly rising pulse rate and alarming drop in blood pressure. Direct examination revealed a very flabby uterus filling with blood, and reaching the diaphragm. Large amounts of blood were expressed; but despite intravenous ergotrate, massage and application of hot towels to the uterus, it failed to contract and the radial pulse became imperceptible.

Meanwhile an intravenous infusion of 10 per cent glucose in saline was started, and within a few minutes 700 c.c. of whole blood was transfused directly from the husband. Supravaginal hysterectomy with removal of the remnant of left adnexa was done and an attempt made to spare the right adnexa. Because of active bleeding in the mesosalpinx, the tube had to be secondarily removed but the right ovary was conserved. The operating time for the three procedures was two hours. A second blood transfusion of 500 c.c. was given after the patient was returned to her room. The wound again healed by primary union and the

## DISCUSSION

DR. MELVIN L. STONE.—In the Laboratory of Gynecological Pathology at Bellevue Hospital we have seen, incidental to routine study of material removed at operation, many instances of adenomyotic foci ranging from minute incursions of the glands of the endometrium into the muscle, to more extensive foci of adenomyosis which are completely removed from the endometrium. These have been noted especially in fibroids and in many other conditions, but we have never seen a case producing uterine atony. We have, however, noted a similar case which I would like to describe to you. The patient in question was a woman of 25 years who had had no pregnancies prior to her admission to Bellevue Hospital in labor. She was at term at the time and was having pains every ten minutes. We examined her and could find nothing very obviously wrong except that she had a very marked cystitis and complained grievously of dysuria because of this. About four or five hours after admission the blood pressure dropped rather markedly, the pulse became imperceptible, the skin became cold and clammy and the uterine contractions ceased. The fetal heart could not be heard. Under the diagnosis of ablatio placentae the patient was subjected to operation. At first glance, when the peritoneal cavity was entered, nothing remarkable was noted. The uterus was distended to the size of a full-term pregnancy and appeared perfectly normal otherwise.

On palpating the uterus posteriorly, however, we felt a cystic mass which we thought was blood clot, inasmuch as there was about 1,000 c.c. of fluid blood in the peritoneal cavity; after removing the fetus, and delivering the empty uterus through the incision, we were rather surprised to find a rupture about 5 cm. in length on the posterior surface of the uterus, through which collapsed membranes were protruding. We removed the uterus and the patient made an uneventful recovery, following transfusions and the usual after-care.

Examination of the uterus from its inner surface revealed a deep crevice in its left side and cornu. This area was ragged and bluish red in color and through it the perforation had occurred. The thickness of the uterine wall throughout the extent of the crevice was about 0.5 cm. in contrast to the thickness of the remainder of the wall which was 3 or 4 cm. This observation verifies the statement which Dr. Molytoff made relative to the destructive effect of endometrial stroma and glands on myometrium.

Microscopic sections, taken through the perforated area, showed a marked decidual reaction which had taken place in islets of ectopic endometrium and throughout the uterus many other such endometrial islands were observed.

It is of interest, as Dr. Sackett stated, that a case such as this was described by Dr. Richardson in 1919 some time before the general recognition of endometriosis as an entity. Dr. Richardson was of the belief that the endometrium, after it had undergone decidual change, possessed some unique power which enabled it to proliferate and invade muscle tissue. It seems, in view of our later knowledge of the subject, that this also was a classical case of endometriosis and that the decidual reaction which he observed was a secondary effect of pregnancy on ectopic endometrial foci.

DR. LEON MOTYLOFF.—It is not generally appreciated that adenomyosis of the uterus is a destructive condition. The endometrial foci in adenomyosis consist of glands and stroma. The glands are usually harmless, but the stroma may be extremely aggressive. It was found by Robert Meyer in 1923 that the stroma of the endometrial islets destroys the myometrium, and he found destruction not only of the interstitial tissue, but also of the most important elements of the muscle cells, the so-called myofibrils, which are responsible for the function of muscle.

Fortunately, not all cases of endometriosis are alike, as is evident from clinical experience. Some of the cases show quite an extensive menorrhagia and others do not. Perhaps the most aggressive types of endometriosis are the recent cases with very cellular stroma. In Dr. Sackett's case the stroma was very cellular which is why it showed such decidual reaction. All the cases that have been reported where the combination of adenomyosis and atony were found, presented such an extensive decidual reaction.

The myometrium was pale, its cut surface looked like a sponge and presented a network of wide spaces which appeared empty on dissection. There was no interstitial hemorrhage.

*Microscopically.*—The remnants of decidua were scant or completely missing in most sections. The myometrium had the appearance typical of pregnancy. There was no evidence of inflammation nor of vascular wall changes. Sections through the old cesarean scar showed fibrosis *without any other pathologic change*.

The submucous layer of the myometrium contained many large foci of adenomyosis. The stroma of the endometrial islets showed marked decidual reaction, while the glandular elements were so extensively proliferated as to form small cysts. The foci were so numerous and so large as to cause dissociation of the muscle fibers in the myometrium (Figs. 1 and 2).

*Diagnosis.*—Puerperal uterus; adenomyosis interna uteri with pronounced decidual reaction; edema and congestion of tube.

### DISCUSSION

In view of the normal uterine behavior at first cesarean section even after thirty hours of active labor, it was difficult to explain the profound atony, hemorrhage, and shock following the second cesarean. The latter was done by election, at term, under ideal conditions, and with no new technical difficulty. In both cases nitrous oxide and ether anesthesia by the closed method was well taken. The operative technique was the same except for time taken to excise the skin scar. Since the second baby was only 12 ounces (340 Gm.) heavier than the first, and since no labor was allowed, the sacculation of the uterine wall was probably no greater and possibly less than before. In standard textbooks sacculations<sup>5</sup> is reported as a cause of dystocia and uterine rupture but not post-partum atony.

Normal afebrile convalescence from the first cesarean section and the appearance of the uterus at the second operation both indicate that the intrinsic muscular, vascular, and nerve structure had been damaged little, if at all. The old scar showed no endometriosis or other demonstrable weakness.

There had been no intercurrent illness. But the menses had become more painful and prolonged, and the cycle varied from thirty-five to forty-two days. This, and the delay of conception for twelve months after the last use of contraceptives, could have been due to adenomyosis of the uterus.

The extensive invasion of the myometrium by endometriosis in the present case seems the most likely cause of the atony and hemorrhage. In the so-called Couvelaire uterus, dissociation of the muscle fibers by extravasated blood is believed to destroy their contractile power. Whether similar dissociation by endometrioid islets is extensive enough to cause post-partum atony and hemorrhage cannot yet be definitely stated. In four cases from the literature, it seemed the obvious cause of spontaneous uterine rupture, even in the first pregnancy in one of them. In Schweitzer's case as well as the present case, it seemed the most obvious cause of atony after cesarean section.

### CONCLUSION

A case is presented of elective repeat cesarean section for sacculation pregnancy followed by uncontrollable uterine atony and hemorrhage requiring removal of the uterus and treatment of shock. The possible causative factors are reviewed and the opinion offered that widespread adenomyosis of the myometrium interfered with its normal contraction and prevented its response to oxytocic drugs.

### REFERENCES

- (1) Stone, M. L.: AM. J. OBST. & GYNEC. 35: 883, 1938.
- (2) Batizfalvy, J.: Zentralbl. f. Gynäk. 63: 40, 1939.
- (3) Schweitzer: Ibid. 51: 938, 1927.
- (4) Szenes, A.: Arch. f. Gynäk. 134: 546, 1928.
- (5) Bumm, E.: Grundriss z. Studium d. Geburtshilfe, ed. 15, Munich, 1922, J. F. Bergman, p. 350.

When the patient began to menstruate several days later, a second vaginoscopy was immediately performed, and blood, mixed with pus, was seen issuing from the sinus opening to the left of the cervical os. At this time, no blood was, as yet, issuing from the cervix itself. The blood from the sinus opening was collected, centrifuged, fixed, and sectioned (Fig. 2), according to the method suggested by Dr. Geist, for determination of menstrual blood. It was reported as consisting of blood, leucocytes, and endometrial epithelium.



Fig. 1.



Fig. 2.

Fig. 1.—Secretion aspirated from sinus opening, showing pus cells and squamous epithelium.

Fig. 2.—Menstrual blood and pus aspirated from sinus opening, showing endometrial glands.



Fig. 3.—A ureter catheter threaded into the orifice in the vaginal fornix, coiled up in the cavity.

On the following day menstrual blood was also seen issuing from the cervix. The hymen was then dilated to admit a speculum, and a ureter catheter was threaded into the sinus opening. X-ray picture showed it to be coiled up in a cavity paralleling the upper three-fourths of the vagina (Fig. 3). Hippuran was injected, and an x-ray picture taken, outlining the cyst (Fig. 4). A sound passed into the uterus showed a uterus deflected to the right side of the pelvis (Fig. 5).

## LATERAL PYOCOLPOS, DOUBLE UTERUS, CERVIX, AND VAGINA, WITH ABSENCE OF LEFT KIDNEY\*

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THIS case of lateral pyocolpos, with double uterus, double cervix, and double vagina, associated with absence of one kidney, is being reported because of its clinical interest, and particularly to emphasize the importance of accurate pre-operative diagnosis.

The patient, L. M., was a white virgin, 25 years of age. The family history was negative. Menstruation had started at 12½ years, was always regular, occurring every twenty-eight days, profuse in amount, and lasting eight days. There was no intermenstrual bleeding. Dysmenorrhea was present on the first day of each menstruation.

At the age of 17 years, the patient noticed a foul, yellowish discharge. This illness was gradual in onset, and not accompanied by chills or fever. The discharge persisted and increased, particularly before the menstrual flow.

At the age of 24, one year ago, she first experienced pain, and a sensation of heaviness in the left lower quadrant. This interfered with walking, occasionally with sleep. At the time of her menses, there was pain in the right leg. There were no urinary symptoms.

Four months ago she was admitted to another hospital, at which no diagnosis was made, and she was discharged with the recommendation to take douches. She then went to the Consultation Clinic at Mount Sinai Hospital, where it was thought that she might have a complex congenital anomaly, and further hospital investigation was advised. She was admitted to the gynecological service of Dr. Geist, to whom I am indebted for the privilege of investigating this case.

Physical examination showed a young, white woman, not acutely ill, fairly well developed. There were no gross stigmas of a glandular disturbance. The general examination was negative; blood pressure was 96 systolic, 66 diastolic; the hemoglobin was 86 per cent. There were 18,800 white blood cells with 53 per cent polymorphonuclear leucocytes. Urine examination was negative. The Wassermann test was negative, the sedimentation time was one and one-half hours. The vaginal smear showed many leucocytes and cocci in chains.

Pelvic examination showed a virginal introitus. There was a profuse, foul-smelling vaginal discharge. Upon rectal examination, the cervix seemed normal in size. The fundus could not be differentiated. The right adnexa seemed normal. To the left there was a cystic mass, the size of an orange, bulging toward the vagina and extending upward and laterally. This was slightly tender. Capping this mass, there was a second, smaller mass in the left lower quadrant. Pressure upon the cystic mass increased the vaginal discharge.

Intravenous pyelogram failed to show any shadow of the left urinary tract. Methylene blue, given by mouth, did not discolor a gauze strip placed in the vagina. Vaginal smears were negative for tubercle bacilli.

Cystoscopy was performed, at which time the right ureteral orifice was easily catheterized; there was no opening to correspond to the left ureter. Indigo carmine appeared on the right side only. The vagina was inspected with a narrow proctoscope. A cervix was seen, and the os was normal. One-half inch to the left of this there was the opening of a sinus, from which pus exuded. This was of the size of a ureteral orifice and led to a tortuous tract. The right lateral fornix was well defined; the left fornix was apparently absent, the cervix merging into the left vaginal wall. Microscopic examination of the pus aspirated from within the sinus opening showed pus cells and squamous epithelial cells (Fig. 1).

\*Presented at a meeting of the New York Obstetrical Society, November 12, 1940.



cervix (right), at a slightly higher level, a second cervix was seen, about two-thirds as large as the right cervix. Its os was patent, easily sounded, and the corresponding uterus was turned to the left. The stump of the septum was between the two cervices.

Cannulas were inserted into both uteri, and simultaneous bilateral hystero-grams were made (Fig. 7). This proved the diagnosis of double uterus, double cervix, and double vagina with lateral pyocolpos due to atresia of the lower end of the left vagina, the anomaly being accompanied by the complete absence of the left kidney.

Fifteen days postoperative, the patient began to menstruate, and menstrual blood was seen issuing from both cervices. At this time, both uteri were easily palpated, freely movable, and there were no adnexal masses. The patient was discharged completely well three weeks after operation.

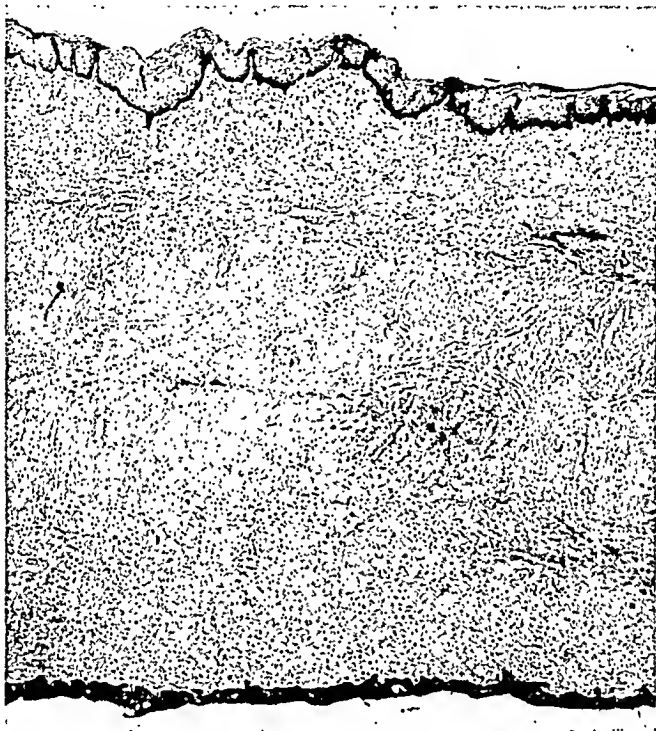


Fig. 6.—Resected septum showing fibromuscular septum lined on both sides with vaginal epithelium.

Follow-up examinations at frequent intervals for over one-half year showed the patient in excellent health, symptom-free, without vaginal discharge. The introitus was normal. A small ridge, 0.5 cm. thick, was present along the posterolateral wall. The mucosa of the left side of the vagina was normal. The cervices appeared normal, and the uteri seemed normal in size. There was no adnexal mass or tenderness.

The case cited is one of failure of complete fusion, with an incomplete breaking through of the left vagina. Arrests of development at this period have the highest correlation with kidney anomalies, including absence of one kidney supposedly due to the impossibility of the ureter bud meeting the definitive kidney anlage.

The clinical picture of the anomaly seen in our patient, as described by numerous authors, is quite characteristic. The patent half of the vagina seems quite normal, although somewhat narrow. The uterus appears to be pushed to one side. To the other side, there is felt a cystic mass extending toward the vulva, and bulging into the normal vagina. In most cases, the cystic mass simulates a low-lying intra-abdominal cyst, and is often capped by a second mass

The sinus opening was now dilated with graduated sounds, and the cystic cavity (lateral pyocolpos) regularly irrigated. The discharge diminished rapidly, pain disappeared, and the patient felt greatly improved. When the return from the irrigation became almost clear, operation was performed.



Fig. 4.—A sound is in the right uterus. Hippuran has been injected through the catheter and outlines the atretic left vagina. Some excess hippuran is seen in the right vagina.



Fig. 5.—Right hystero-gram showing position of the right uterus and the tube. The uterotubal angle is well demonstrated.

*Operation.*—Under general anesthesia, the vault of the vagina was exposed, a cannula inserted into the sinus opening, and the lateral pyocolpos flushed with saline solution. When the return was clear, the cavity was distended with fluid by means of a cannula fitted with an appropriate obturator. The most inferior portion of the distended cavity, one-half inch above the hymen, was aspirated with a 20-gauge needle, and a window made at this point. A good portion of the septum between the sinus opening and this window was then excised, and complete drainage established. The vagina, now converted into a single space, was packed.

Pathologic examination of the wall showed "fibromuscular septum covered on both sides by squamous epithelium" (Fig. 6).

Within a week all discharge had stopped. The wall of the cyst now had the appearance of normal vaginal epithelium. To the left of the previously noted

standpoint of possible injury to the remaining ureter as a result of misguided operative interventions.

The etiology of the infection which converts a lateral hematocolpos into a pyocolpos is not always clear. The stagnation of menstrual blood furnishes an excellent culture medium, and the opening in the septum, primary or secondary to rupture or manipulation, may furnish the point of entry of bacteria. In most instances, the secretion had a foul odor. This was true in our own case.

#### SUMMARY

1. A case of lateral pyocolpos is described, in which there was a double vagina, double cervix, and double uterus, with atresia of the lower end of the left vagina. This genital anomaly was associated with the absence of the left kidney.

2. Complete diagnosis of the condition preoperatively facilitated the extremely simple therapy.

3. Treatment recommended is preliminary cleaning up of the infection by irrigation, followed by removal of the septum between the two vaginas.

4. Points of importance in the investigation are the examination of the secretion from the lateral cyst, the use of contrast media in the pyocolpos and uterus, the determination of endometrium in the menstrual blood aspirated from the cavity, and the investigation of the genitourinary tract.

I wish to express my thanks to Dr. Geist for the privilege of investigating this case.

### HYDATIDIFORM MOLE FOLLOWED BY CHORIONEPITHELIOMA\*

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(From the Germantown Hospital)

IT IS striking that the conditions of hydatidiform mole and chorionepithelioma are reputedly of such infrequent occurrence, and the sequence of epithelioma following mole is of even more rare occurrence.<sup>1-6</sup> I believe that a greater number of these tumor cases exist than is generally assumed, and that they are treated in the surgical wards of hospitals where gynecology is included under surgery. Two such cases, the occurrence of which might otherwise have passed unrecorded, are reported herewith.

CASE 1.—E. A. (20955), a colored woman, aged 38 years, was admitted to the Surgical Service of Germantown Hospital Jan. 29, 1936. The relevant portion of her history is as follows: She had missed four periods, was believed to be pregnant, and began to bleed. The diagnosis was "incomplete abortion." She was curetted and large amounts of grapelike masses were obtained which were grossly and microscopically diagnosed "hydatidiform mole." Five days later the patient was re-operated upon and a subtotal hysterectomy, bilateral salpingectomy, and right oophorectomy were done. The uterus was slightly larger than normal, the right ovary being cystic. The left ovary (not removed) appeared to be normal. The pathologic report was as follows: "Uterine canal is soft and boggy and occupying half of the fundus is a large irregular mass of soft friable tissue mixed with considerable blood clot. This appears to have penetrated the endometrium in several places."

Microscopic sections of the uterus revealed a "chorionepithelioma, early with slight penetration" and "chronic interstitial oophoritis with corpus luteum cyst and luteoma." No ovarian metastases were seen.

\*Presented at a meeting of the Philadelphia Obstetrical Society, January 2, 1941.

which proves to be the uterus. Not infrequently, a small communication in the upper part of the septum between the two vaginas permits more or less intermittent discharge of blood or pus.

The diagnosis, however, was not made preoperatively in the majority of cases. As a consequence, a great many of the reported cases were diagnosed only following laparotomy or extensive vaginal dissections.

Jaschke and Pankow in 1933 were enabled to make the diagnosis preoperatively by finding squamous epithelium in the secretion. They emphasized the difficulty in diagnosis, and considered a differential diagnosis between this condition and parametrial abscess almost impossible.

In many instances, quite unnecessary hysterectomies were performed, and equally unnecessary total excisions of the supposed vaginal cysts. Obviously, the procedure of choice is the simple one of extirpating a large portion of the septum, preferably after preliminary cleaning up of infection.



Fig. 7.—Double hystero-gram showing both uteri, both tubes. The uteri are laterally placed. The cervixes are outlined by hippuran in the vagina, the right at a slightly lower level than the left.

The condition should be suspected in the presence of lateral vaginal cystic masses, or discharges of an obscure nature from vaginal sinuses. The swelling does not always parallel the side of the vagina, and often runs a semispiral course, arising posteriorly and bulging into the abdomen and above Poupart's ligament. This is one of the factors that contributes to difficulty in diagnosis and is misleading.

Once the possibility of such a condition is entertained, we have at our disposal adequate measures to investigate such a case completely. These include, in addition to the ordinary gynecologic examination, the study of the secretion from such sinuses, the catheterization of the pockets, x-ray study with contrast media, and x-ray examination of the uteri. An apparently complex technical problem can thus be converted into a very simple one.

The differential diagnosis from other vaginal cysts, including Gärtner's cyst and cysts of the vagina due to misplaced ureters, is made easy.

All such cases, as well as all other anomalies of the genital tract, should have the benefit of a urologic investigation, including intravenous pyelography, because of the surprisingly frequent association with the absence of one kidney. Over one hundred cases of this association have been reported. According to Ballo-witz, in 213 cases of absent kidney, there were 71 females, of whom 41 had anomalies of the genitalia. The frequency of absent kidney is about 1 in 3,000. Up to 1916, 94 cases of absent kidney are in the literature, collected by W. Reusch. This is of scientific interest, and also of clinical importance from the

malignant as it has been pictured, there is some justification for this stand. This feeling is more understandable too when the patient is near the menopause as was true here. Certainly the decision to re-operate proved fortunate in this instance. A second point is the fact that the operator felt safe in leaving a normal appearing ovary, and time proved he was right in so doing. Third, microscopic sections of the cystic ovary showed no evidences of metastases, adding to the accumulated evidence which tends to show that metastases or extensions from uterus to ovary are rare or never occur. Fourth, while used in an elementary way, the two successive negative qualitative Friedman tests added assurance to the belief that the tumor had been completely removed.

The second case also brings up some interesting points: the use of biologic tests, the value of histologic sections, and the soundness of clinical observations. The qualitative Friedman test done before curettement simply indicated the presence of pregnancy tissue and nothing more. The same test, though positive, taken two weeks after curettement meant nothing because slowly dissolving benign chorionic tissue might still be giving a positive qualitative test. It might even be giving a very high quantitative prolan reading at this time. To base one's decision to do a hysterectomy on persistently positive qualitative Friedman tests in the period immediately following molar evacuation will mean sacrificing of many normal uteri. If these biologic tests are to have value, they must be quantitative, must be taken at frequent intervals, and the values plotted on a graph.<sup>7-10</sup> A steadily falling prolan curve bespeaks benign tissue (Payne); a rising curve, the reverse. Return to normal usually takes eight to twelve weeks.<sup>11, 12</sup>

The curetted tissue was not of great help because no specimen included the molar—uterine junction, and invasion could neither be demonstrated nor ruled out. To secure the most desirable tissue, direct excision by hysterectomy<sup>3</sup> or a careful selection of the last of the curetted fragments must be done. If a suitable specimen can be secured, histologic diagnosis of chorionepithelioma is feasible despite the opinions of many to the contrary.<sup>9, 10, 12</sup> Chorionepithelioma was readily diagnosed in the sections taken from the extirpated uteri and the diagnosis confirmed by more than one competent pathologist.

Clinical findings really brought this patient to her second and life-saving operation. Persistent, then enlarging, ovarian masses, and re-enlargement of the uterus are very strongly suggestive, in this situation, of the presence of actively growing chorionic tissue. Another clinical sign, not noticed here, is the reappearance of uterine bleeding. Where prolan estimation and histologic section are not available, these clinical signs alone would call for a second curettement, a hysterotomy, or possibly even a hysterectomy.

The operator in Case 2 held the opinion that if malignancy be present in the uterus then both adnexa should be completely removed, so that these possible sites for extension or near-by metastases may be eliminated. Whether these adnexal structures appear normal or abnormal is beside the point. So the huge cystic ovaries, made so by the many lutein cysts whose fluid is rich in prolan, were removed. Many gynecologists believe such ovaries are completely benign and will return to normal after the stimulator of prolan production, the chorionic tissue, is removed. All<sup>9, 13, 14</sup> admit of the possibilities of hemorrhage from and torsion of such cystic ovaries. In the present instance, histologic section of the

The patient had an uneventful convalescence. Qualitative Friedman tests were done one month and three months after operation and were negative. The patient is well and has negative pelvic findings four years after her discharge.

CASE 2.—C. T. (24534), white, married, was admitted Dec. 20, 1938, to the Surgical Service at Germantown Hospital giving the following story. Her last regular period was two months previous. She noticed a mass in her abdomen which had increased in size, and two weeks before admission vaginal bleeding began and continued off and on, being at first slight, then becoming heavier two days before entering the hospital. Examination showed a mild generalized jaundice, icterus index being 42. Abdominal palpation revealed an irregular mass extending up to the mid-epigastrium and an "irregular attached mass extending almost to the costal margin on the left." Vaginal examination showed the uterus to be continuous with the mass previously described. Red blood count was 1,970,000; Hg, 30 per cent. A diagnosis of pregnancy was made with the possibilities of (1) incomplete abortion; (2) threatened abortion; and (3) possible hydatid degeneration. On Dec. 22, 1938, a qualitative Friedman test was positive. On the same day after proper preparation (blood, etc.), a curettage was done and typical molar tissue recovered. This was reported pathologically as "benign hydatidiform mole" but a later section showed some active proliferation of cells, but no uterine tissue was included in this section so invasion could not be reported upon.

The patient improved rapidly. The uterus was reduced in size. On Jan. 6, 1939, fifteen days after operation a qualitative Friedman test was positive. Examination on the nineteenth postoperative day disclosed a uterus still about twice normal size and a questionable mass in the right side. Operation was advised but the patient refused and went home. Five days after discharge she began to have abdominal pains and noticed a purulent vaginal discharge. She was re-admitted three weeks after leaving the hospital or forty days after her curettement. At this time the uterus had again enlarged somewhat and the abdominal masses, now bilateral and extending up to the umbilicus, could easily be felt. On Feb. 1, 1939, a total hysterectomy and bilateral salpingo-oophorectomy were done by Dr. S. D. Weeder. The uterus was found slightly enlarged but otherwise normal. Both ovaries were distended to a diameter of about eight inches with large cysts, hemorrhagic in some sections. Pathologic examination showed these to be lutein cysts. They contained fluid rich in prolan. The opened uterus had some adherent and penetrating molelike tissue at the upper left pole. In the upper pole was a quantity of necrotic material. Microscopic diagnosis: "hydatidiform mole and chorionepithelioma."

The patient had an uneventful convalescence. One month and one-half after the hysterectomy, a qualitative Friedman test was negative. The patient has refused further visits but is known to be well, symptom free and working at present, two years later.

#### DISCUSSION

These two cases serve well as texts for a brief discussion. The first case illustrates four points. First the belief held by some that the finding of a mole *ipso facto* calls for a hysterectomy to prevent the growth or spread of the more malignant tumor. If chorionepithelioma is as

## STETHOGRAM AND RECORDED DISC OF FETAL HEART SOUNDS IN A TWIN PREGNANCY

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ONLY a few have succeeded in making photographic records of fetal heart sounds and in some of these the vibrations are very indistinct. Orias and Braun-Menendez<sup>1</sup> state that the recording of fetal heart sounds is very difficult and this explains why so few such studies have been made. In their book on heart sounds two stethograms of fetal hearts made by Pereira are shown and these are very good. Hofbauer and Weiss<sup>2</sup> in 1908 and Beruti<sup>3</sup> in 1923 succeeded in making a few photographic records of fetal heart sounds but the results were very unsatisfactory. Lian, Golblin and Minot<sup>4</sup> in 1938 made graphic records of fetal heart sounds (number not stated) and also cut a few discs. Smith and Hervet<sup>5, 6</sup> in 1940 succeeded in making fetal stethograms and recording reproducible fetal heart sounds on discs in 52 cases. Dressler and Moskowitz<sup>7</sup> in 1941 simultaneously recorded fetal stethograms and electrocardiograms (by the Strassman technique) in 40 cases.

In none of these reports has the recording of twin fetuses been mentioned. In the review of all the medical literature on this subject, no recordings of a twin pregnancy by stethograms or phonographic discs have been found. However, Bell<sup>8</sup> has reported the taking of fetal electrocardiograms in two cases of twin pregnancies, one of these yielding fetal deflections while the other was unsuccessful. Electrocardiograms were taken on 33 pregnant women, and in 10 of these fetal heart R-waves were registered.

### CASE REPORT

Primipara, 24 years of age, was admitted to the hospital on Oct. 14, 1940. On physical examination a diagnosis of twins was made and two fetuses were seen in the roentgenogram. The first fetus (No. 1) filled the right side of the abdomen, the head was in the pelvis and the back on the right. The head of the second fetus (No. 2) was seen in the left lower abdomen and the back above it was curved laterally.

The heart sounds of the first fetus were easily heard through the stethoscope in the right lower abdomen, but the sounds of the second fetus could not be found. So the problem was to know whether the second fetus was living or not.

Fetal stethograms, cardiophonograms, and electrocardiograms with maternal electrocardiograms and pulse were taken simultaneously. Following this, the maternal heart sounds, electrocardiogram, and polygram were recorded at the same time.

The stethograph used to photograph the heart sounds has been described by Lockhart<sup>9</sup> and the cardiophonograph (Fig. 1) employed to cut the discs of reproducible heart sounds was developed by the author.<sup>10, 11</sup>

The fetal electrocardiographic technique followed was that described by Strassman and Mussey.<sup>12, 13</sup>

removed ovaries showed no malignancy, again adding to the evidence that involvement of these structures by chorionepithelioma is rare.

The dispute over the proper course to pursue with the ovaries brings up the most important question on the whole subject of chorionepithelioma. Just how malignant is this tumor? On the one hand is it the rapidly fatal blood metastasizing super-cancer? Or on the other, is it the tumor whose distant and widespread metastases will disappear after the parent tumor is excised? Is it the tumor which has even been reported to have spontaneously regressed and disappeared itself along with its metastases? Between these two extremes the answers lie for there must either be grades of malignancy as Ewing<sup>15</sup> believes or grades of host resistance as Montgomery<sup>16</sup> believes.

I desire to express my appreciation to Drs. E. B. Hodge and W. B. Swartley for permission to report these cases.

#### REFERENCES

- (1) *Curtis, A. H.*: Textbook of Gynecology, Philadelphia, 1930, W. B. Saunders Co. (2) *DeLee, J. B.*: The Principles and Practice of Obstetrics, Philadelphia, 1925, W. B. Saunders Co. (3) *Schuman, E. A., and Voegelin, A. W.*: AM. J. OBST. & GYNEC. 33: 473, 1937. (4) *Sherman, J. T.*: Am. J. Surg. 27: 237, 1935. (5) *Mathieu, A.*: AM. J. OBST. & GYNEC. 57: 654, 1939; also Novak's discussion. (6) *Mathieu, A.*: Surg., Gynec. & Obst. 64: 1021, 1937. (7) *Zondek, B.*: J. A. M. A. 108: 607, 1937. (8) *Brindeau, A., Hinglais, H., and Hinglais, M.*: Gynec. et obst. 40: 208, 1939. (9) *Mathieu, A.*: Surg., Gynec. & Obst. 64: 1121, 1937. (10) *Payne, F. L.*: Paper unpublished. (11) *Kimbrough, R. A., Jr.*: AM. J. OBST. & GYNEC. 28: 12, 1934. (12) *Mazer, C., and Goldstein, L.*: Clinical Endocrinology in the Female, Philadelphia, 1932, W. B. Saunders Co. (13) *Meigs, J. V.*: In discussion of Mathieu.<sup>5</sup> (14) *Smiley, J., and Clements, A. B.*: AM. J. OBST. & GYNEC. 10: 471, 1940. (15) *Ewing, J.*: Quoted by Wilson, K. M.: AM. J. OBST. & GYNEC. 38: 824, 1939. (16) *Montgomery, T.*: In discussion of Mathieu.<sup>5</sup> AM. J. OBST. & GYNEC. 57: 654, 1939.

#### DISCUSSION

DR. EDWARD SCHUMAN.—Lutein cysts of the ovary, accompanying hydatid moles or chorionepithelioma, represent a lutein reaction to the tremendous amount of gonadotropic substance elaborated by the chorionepithelioma. There has been some question in my mind as to whether the ovaries should routinely be removed in the presence of this disease. They are very rarely the seat of metastasis and there usually remains some doubt about the malignancy of chorionic tumors at the time of operation.

With regard to the fallibility of the hormone tests in the presence of mole or chorionepithelioma, Dr. Voegelin and I reported a case in which Aschheim-Zondek tests were negative for something over a year, while the patient was suffering from chorionepithelioma. These tests did not become positive until a month before the patient's death.

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Itoh, R.: Determination of Sex of Fetus, Zentralbl. f. Gynäk. 64: 1302, 1940.

The author claims successful prediction of sex in 15 cases. Using the maternal urine, Itoh extracted it with acetone and ether, combining the resulting fraction with an acetone-ether extracted fraction of dog testes. The effect of a proteolytic ferment, which the author claims is secreted by the fetal testes, will be to elevate the amino-nitrogen content of the above mixture, while a low aminonitrogen value will be obtained in the case of female fetuses.

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## STETHOGRAMS

*First Fetus (No. 1).*—These heart sounds were taken through the lower right abdominal wall and over the back of the first fetus. The second sounds were of greater intensity than the first. The first sounds were made up of two vibrations, while the second consisted of four cycles and appeared to be split. Systoles varied in duration from 0.19 to 0.22, and diastoles from 0.23 to 0.26 second. The rhythm which varied somewhat was of sinus origin and the rate averaged 129 per minute.

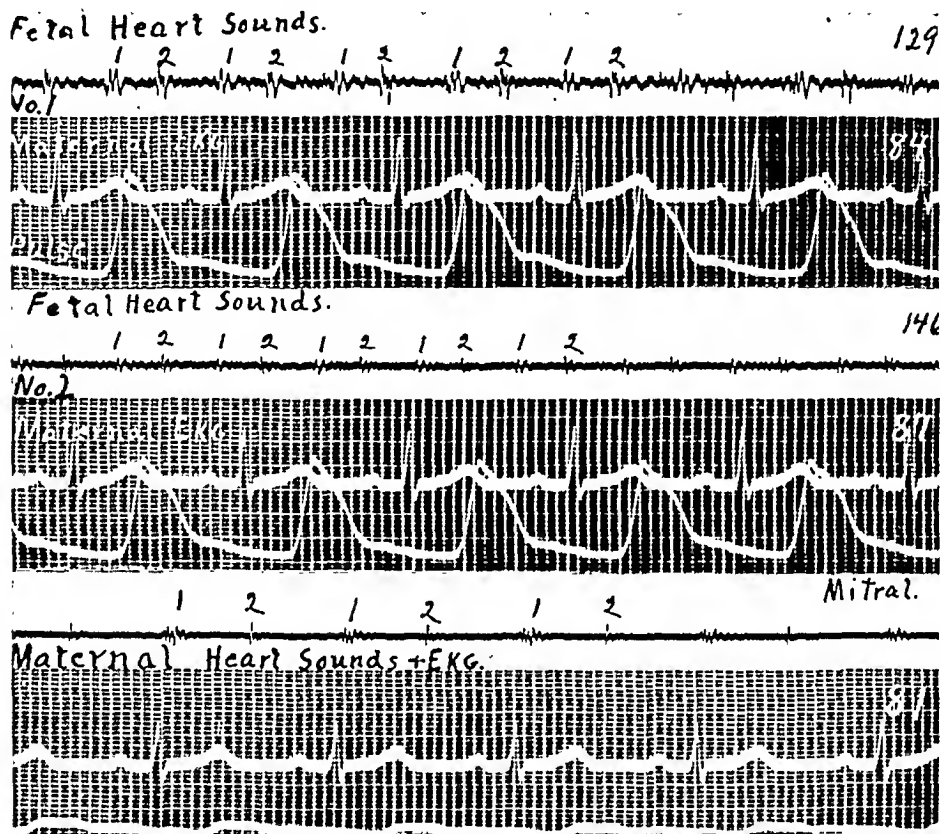


Fig. 3.—Upper. Heart sounds of fetus No. 1 with a rate of 129. Maternal electrocardiogram (Lead I) and pulse. Middle. Heart sounds of fetus No. 2, the heart rate is 146. Maternal electrocardiogram (Lead I) and pulse. Lower. Maternal mitral heart sounds, electrocardiogram (Lead I), and pulse. Each group is taken simultaneously.

*Second Fetus (No. 2).*—This stethogram was taken over the mid-lateral left abdomen and the back of the second fetus. The sounds were of low intensity, while the vibrations were slow in the first (1) and more rapid in the second (2). The duration of systoles was 0.17 to 0.19, and diastoles 0.21 to 0.22 second. The sinus rhythm was almost regular, while the rate averaged 146.

*Mother.*—The heart sounds were of low and about equal intensity over the apex. The first was of much longer duration than the second. No murmurs were heard, and the diastole (0.38 second) was longer than the systole (0.32 second). The rate varied from 81 to 87.

## ELECTROCARDIOGRAM AND POLYGRAM

The electrocardiogram and pulse were those of the mother and were taken simultaneously with the heart sounds in each case. No fetal waves were seen in the electrocardiogram.

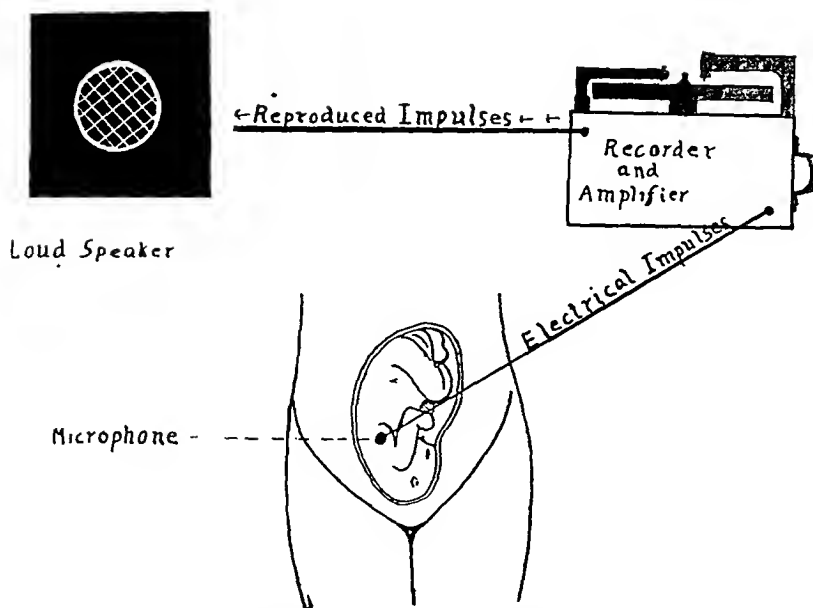


Fig. 1.—Diagram of method of making recorded discs and auditing heart sounds from records or directly from the fetal heart.

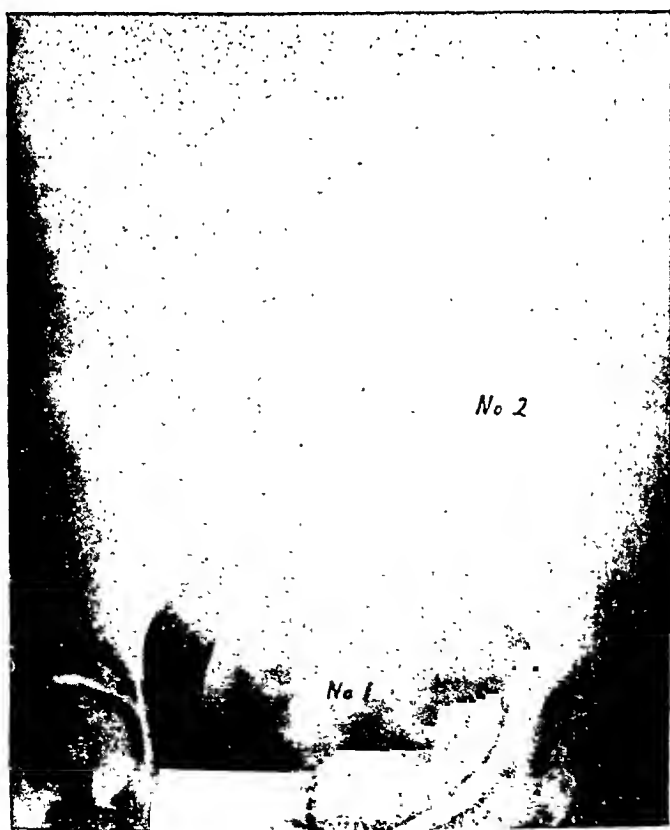


Fig. 2.—Roentgenogram of twin fetuses. No. 1 right lower and No. 2 left upper.

## THECA CELL TUMOR OF OVARY AND ENDOMETRIAL CARCINOMA

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THECA cell tumors of the ovary are comparatively rare, since Dockerty in 1940 was able to collect only 25 cases from the literature, to which he added 10 more. In the same year, 6 more cases were reported by various authors.

The first 6 examples of this tumor were described by Loffler and Priesel in 1932, under the name "fibroma theco-cellulare xanthomatodes." Undoubtedly there are more cases which have gone unrecognized, possibly due to the close similarity of the histologic picture of this tumor to the ordinary fibroblastoma.

Traut and Butterworth studied a group of mouse ovarian tumors which had been artificially produced with x-rays by Furth and Butterworth. They were able to trace the origin of theca cell, granulosa cell, and lutein cell tumors. There was also definite evidence that the tumors were physiologically active. It has also been shown by various investigators that blood of patients with theca cell tumors contained increased amounts of estrin.

The following case interested us because of the associated adenocarcinoma of the endometrium. Most of these tumors produce uterine bleeding, which results from endometrial stimulation caused by estrin secreted by the tumor. However, when such a tumor is found in individuals who have not reached the menopause, there is usually amenorrhea. In the following case we feel that the association of the two neoplasms is more than coincidental.

### CASE REPORT

L. K., a 72-year-old female, was referred to the hospital because of occasional small amount of vaginal bleeding over a period of two years. Except for an occasional heavy, bearing-down sensation in the pelvis, there had been no other symptoms. The bleeding had never been profuse, but had been rather constant. During this time she gained a small amount in weight, and except for past history of occasional attacks of arthritis, her medical history was negative. Menstrual history was normal and uneventful. The menopause occurred at the age of 55 years, and there had been no bleeding up until two years ago.

Physical examination showed a well-developed and well-nourished white woman of 72 years, showing atrophic arthritic changes of the joints of hands, wrist, and ankles. Heart and lungs were normal; thyroid was not enlarged. Breasts were well-developed, pendulous, slightly atrophic; no masses were palpated. Abdomen was obese, soft, and no masses or tenderness was made out. Pelvic examination: vagina atrophic; there was some whiteness about the labia, suggestive of leucoplakia. The cervix showed a very small polyp protruding from the external os. The

## RECORDED HEART SOUNDS

Those of the first fetus when reproduced were loud and clear and of equal intensity, the rhythm varied considerably, and a soft uterine souffle could be heard. The movement of the fetus was clearly audible.

The sounds of the second fetus were partly neutralized at times by the uterine souffle. They were softer in character than the first and varied in rate and rhythm. Movement of intestinal contents could be heard at times.

In the maternal sounds the first was of greater duration than the second, but they were about equal in intensity. No murmurs were audible, but the respiratory sounds were distinctly heard.

A diagnosis of live twin fetuses with normal hearts was made.

Two normal babies were born on Nov. 1, 1940, and the heart rate of No. 1, which was born first, was slower than that of No. 2.

## SUMMARY

A stethogram of twin fetuses and the disc recording of these heart sounds, which could be audited when desired, are reported.

A twin pregnancy in which there was a question of viability of one fetus is described.

The stethogram and recorded disc of the twin fetal heart sounds made the positive diagnosis of two live fetuses, and this was confirmed by the birth of two normal babies.

This is believed to be the first stethogram and disc recording of twin fetal heart sounds reported in medical literature.

I wish to thank Dr. W. J. Hervert for the opportunity to study this case.

## REFERENCES

- (1) *Orias, O., and Braun-Menendez, E.*: The Heart Sounds in Normal and Pathological Conditions, Oxford University Press, 1939, p. 135.
- (2) *Hofbauer, J., and Weiss, O.*: Zentralbl. f. Gynäk. 22: 429, 1908.
- (3) *Beruti, J. A.*: Rev. espan. obst. y ginec. 8: 516, 1923.
- (4) *Lian, C., Golblin, F., and Minot, G.*: Bull. Soc. Gynec. et d'obst. 27: 423, 1938.
- (5) *Smith, A. L., and Hervert, W. J.*: AM. J. OBST. & GYNEC. 40: 102, 1940.
- (6) *Smith, A. L.*: Read at the Sixteenth Scientific Sessions of American Heart Assoc., June 7, 1940.
- (7) *Dressler, M., and Moskowitz, S. N.*: AM. J. OBST. & GYNEC. 41: 775, 1941.
- (8) *Bell, G. H.*: J. Obst. & Gynaec. Brit. Emp. 45: 802, 1938.
- (9) *Bierring, W. L., Bone, H. C., and Lockhart, M. L.*: J. A. M. A. 104: 628, 1935.
- (10) *Smith, A. L.*: The Merck Report, April, 1941, p. 6.
- (11) *Smith, A. L.*: Medical Times 69: 243, 1941.
- (12) *Strassman, E. O., and Mussey, R. D.*: AM. J. OBST. & GYNEC. 36: 986, 1938.
- (13) *Strassman, E. O.*: Proc. Staff Meet. Mayo Clinic 11: 778, 1936.

134 SOUTH THIRTEENTH STREET

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Peller, E.: Sebaceous Glands in the Cervical Mucosa, Zentralbl. f. Gynäk. 64: 1258, 1940.

A 40-year-old woman complained of a yellowish, occasionally bloody vaginal discharge of four weeks' duration. Colposcopic diagnosis of sebaceous glands in the cervical mucosa was made and confirmed microscopically. Small yellow spots could be seen over the portio as the source of the discharge, the glands appearing as small cystic elevations. The author uses colposcopy routinely.

R. J. WEISSMAN

ments. Raw areas were peritonized. The patient made a normal convalescence and was discharged from the hospital Aug. 8, 1940. Since then she has returned to our tumor clinic, and has been doing very well. She has no pelvic symptoms and pelvic examination has been negative throughout.

*Pathologic Examination.*—Uterus was enlarged, measuring 8 cm. in length, 7 cm. in width, and 3 cm. in depth. The uterine cavity was occupied by a soft, friable, reddish-purple mass, which was attached by a wide base to the endometrial surface. The mass extended for some distance into the myometrium. In addition, there was a small intramural fibroid 2 cm. in diameter. The right ovary had been replaced by a solid, encapsulated, bright yellow, firm mass measuring 4 by 2 by 2 cm. The left ovary measured 14 by 1 by 1 cm. and contained small follicle cysts.

Microscopic examination of the uterine tumor revealed structure composed of irregular glands lined by low columnar cells (Fig. 1), which showed no evidence of secretory activity. The interglandular stroma was scant and almost absent in places. The tumor invaded the myometrium for a short distance. The adjacent endometrial glands were greatly and irregularly dilated, but there was very little stromal activity.

The ovarian tumor (Fig. 2) was composed of closely-packed, small, elongated or oval cells, which occasionally are arranged in wide, sweeping bundles, and elsewhere form small interlacing networks. The intercellular substance was pale and scant. Fine fibrils were seen with Mallory's phosphotungstic acid stain and Masson's trichrome. Searlet R brings out the numerous fine, fat droplets in practically all cells and stroma.

*Comment.*—This case is characteristic of previously reported theca cell tumors of the ovary, and is of special interest because of the associated endometrial carcinoma. While it is not possible to prove that the ovarian tumor was the etiologic agent responsible for the uterine tumor, our knowledge of theca cell tumors and their similarity to granulosa cell tumors would lead one to believe that the physiologic hyperplasia of the endometrium has progressed to a neoplasm. It is generally accepted that the majority of granulosa cell tumors and theca cell tumors secrete estrin. They do cause stimulation of the endometrium, with resultant bleeding. Granulosa cell tumors may occur at any age, while theca cell tumors are usually found after the menopause. In 10 cases of theca cell tumors of the ovary reported by Dockerty, carcinoma of the endometrium was encountered once. This same author found 3 carcinomas of the endometrium in 32 cases of granulosa cell tumors of the ovary.

A case of theca cell tumor of the ovary with an associated carcinoma of the endometrium is presented, in which we feel that it is reasonable to assume that the ovarian tumor played a major role in the production of the uterine tumor.

#### REFERENCES

- (1) Dockerty, M. B.: AM. J. OBST. & GYN. 39: 434, 1940. (2) Löffler, E., and Priesel, A.: Beitr. z. path. Anat. u. z. allg. Path. 90: 199, 1932. (3) Traut, H. F., and Butterworth, J. S.: AM. J. OBST. & GYN. 34: 987, 1937.

uterus was in third degree of retroversion, slightly and irregular enlarged. In the right vault there was an indefinite mass. On May 10, 1940, under gas anesthesia, the cervical polyp was removed and the base cauterized. At that time an attempt was made to dilate the cervix, but no opening could be found from the internal os into the uterus. The patient was discharged from the hospital May 17, 1940, and told to report if she had any more bleeding. On July 24, 1940, she was readmitted to the hospital because of continued vaginal bleeding. On July 27, under gas-ether anesthesia, the abdomen was opened through a low midline



Fig. 1.—High power photomicrograph of the endometrial tumor shows acini lined by columnar epithelium.

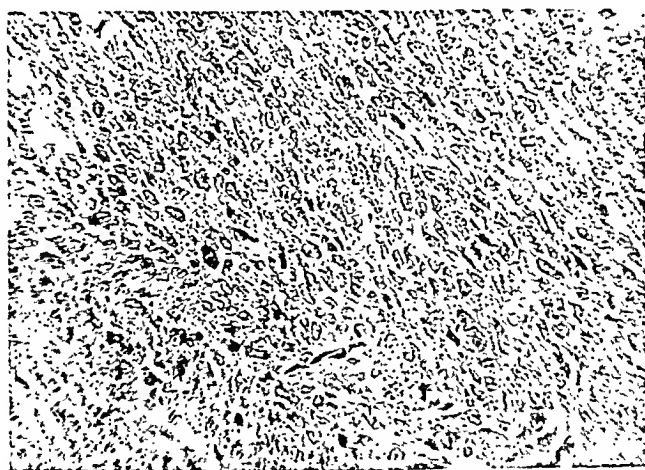


Fig. 2.—High power photomicrograph of the ovarian tumor stained with hematoxylin and eosin. A characteristic field composed of spindle-shaped cells. Lipoid droplets not apparent with this stain.

incision extending from the pubis to the umbilicus. The gall bladder was palpated and found to be filled with small stones. The uterus was approximately four times normal size for a woman of this age, and the left ovary was detached, enlarged, and cystic, lying beneath the uterus in the left portion of the cul-de-sac. This ovarian tumor was apparently without any major blood supply. It was easily removed, after dissecting away the adhesions by both sharp and blunt dissection. The right tube, ovary, and uterus, including the cervix, were then removed. The vagina was closed with interrupted sutures and suspended by the round liga-

# Society Transactions

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## NEW YORK OBSTETRICAL SOCIETY

*MEETING OF MAY 13, 1941*

The following papers were presented:

**Adenomyosis Interna Uteri as a Cause of Uncontrollable Atony and Hemorrhage Following Cesarean Section for Sacculation Pregnancy.** Dr. Nelson B. Sackett. (For original article, see page S94.)

**Functional Studies on the Vascular System of the Kidney in Normal Pregnancy and in Late Toxemia.** Dr. Howard C. Taylor, Jr., and Dr. Irwin Wellen (by invitation). (Will be published in a later issue.)

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## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF APRIL 18, 1941*

The following papers were presented:

**The Evaluation of the Several Types of Cesarean Section and Their Indications.** Dr. Edward A. Schumann, Philadelphia, Pa. (by invitation).

**Indications for the Schumann Type of Cesarean Section.** Dr. Walter W. Coen.

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*MEETING OF MAY 16, 1941*

The following papers were presented:

**Role of Carbon Dioxide in Resuscitation at Birth After Asphyxia and After Nembutal Anesthesia.** Drs. W. F. Windle (by invitation) and R. F. Becker. (For original article, see page S52.)

**Roentgen Pelvimetric Analysis of Walcher's Position.** Drs. Harold M. Brill, and Gerhard Danelius. (For original article, see page S21.)

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## PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

*ANNUAL MEETING, MAY, 24, 1941*

The following paper was presented:

**The Present Status of Endocrinology as It Pertains to Obstetrics and Gynecology.** Dr. Robert T. Frank, New York, N. Y., by invitation.

# INTESTINAL OBSTRUCTION FOLLOWING THE BALDY- WEBSTER SUSPENSION OF THE UTERUS

WILLIAM BICKERS, M.D., RICHMOND, VA.

FREQUENT reference is made in medical literature to intestinal obstruction occurring after suspension operations, but actually there are comparatively few cases reported. Usually this complication is mentioned by the authors only to prove that one type of operation is superior to another. The Baldy-Webster technique is used by many gynecologists on the assumption that it leaves no potential hernial openings in the peritoneal cavity and thus has a certain advantage over other operations. This may be true. The literature does not contain a sufficiently comprehensive study of this very important problem to permit us to draw any conclusion as to which operation is least likely to cause subsequent intestinal complications. In the present state of our knowledge, this most important question cannot be answered. Since it is true, however, that many surgeons use the Baldy-Webster technique on the assumption that it eliminates this potential hazard, the following cases of mechanical obstruction through hernial openings in the broad ligaments are reported.

CASE 1.—D. D., aged 31 years, white, was the mother of three living children. Prior to her last pregnancy the patient had a Baldy-Webster suspension of the uterus for an uncomplicated retroversion. Six months after the operation she became pregnant, enjoyed an uneventful gestation, and delivered a normal female infant at term, following a short, spontaneous labor. The operation did not in any way complicate the pregnancy. Three months after the delivery she was seen one evening with acute pain in the left lower quadrant which was soon accompanied by vomiting. Pelvic examination revealed a normal size uterus in anterior position and a movable, nontender mass in the region of the right adnexa. The patient insisted that her pain was on the left, but in spite of her persistence, a diagnosis of right ovarian cyst with twisted pedicle was made. No mass could be palpated on the left. The patient was removed to the hospital and prepared for operation. On opening the abdomen, a pseudomucinous cyst of the right ovary which was not twisted could be seen and this was removed. Just to the left of the uterus and below the ovarian ligament there was an opening in the left broad ligament through which 10 cm. of the ileum was herniated. The bowel was strangulated but in good condition. The hernia was reduced and the broad ligament opening closed after freeing the round ligament on that side and plicating it in front of the closed opening on the anterior leaf of the broad ligament. Inspection of the opposite side showed a firm adhesion of the round ligament to the broad ligament; no opening could be seen, and it was left in place.

CASE 2.—C. S., aged 19 years, virgin, had a Baldy-Webster suspension at the age of 17 for a retroversion which was thought to be the cause of severe dysmenorrhea. The operation corrected the displacement but not the dysmenorrhea. When the patient was seen two years after the operation, she gave a history of two attacks of acute abdominal pain accompanied by vomiting which had been treated with bed rest and sedation. She stated that in both instances the pain had come on suddenly and left her with the same celerity. It was after the second attack that the patient was referred to me for a gynecologic opinion on the cause of this pain. Examination revealed nothing but a well suspended uterus and normal adnexa. Two days after this examination the patient had another acute attack of pain and at this time the diagnosis was apparent. Clinical signs of hyperperistalsis, pallor, rapid pulse, and intractable vomiting were present. On pelvic examination a mass was palpable in the region of the left parametrium. At operation an interesting situation presented itself. There was an opening in the posterior leaf of the left broad ligament at the site of the round ligament exit through which a loop of ileum had herniated into the left broad ligament and had dissected between the leaves for a distance of several centimeters. The anterior leaf was firmly adherent to the round ligament and presented no opening. The hernia was reduced and the suspension torn down on both sides. The broad and round ligaments were plicated in front of the uterus, thus closing the hernial opening and shortening the uterine supports.



is roughly estimated as the equivalent of 3,000 I.U. (300 gamma) of estrone daily. This calculation is not very far from an estimate, based on clinical trials by W. M. Allen, of 4,200 I.U. daily.

C. O. MALAND.

**Fevold, H. L.: Synergism of the Follicle Stimulating and Luteinizing Hormones in Producing Estrogen Secretion, *Endocrinology* 28: 33, 1941.**

To extend earlier observations of the synergism of the two pituitary gonadotropic hormones (FSH and LH) in initiating secretion of estrogen from the ovaries, Fevold used extracts prepared by previously described methods from sheep pituitaries on normal immature rats.

He concludes that follicle-stimulating hormones are the primary factor in the production of estrogen in the rat, in that it initiates secretory activity. Luteinizing hormones alone cannot initiate, but augment the action of follicle-stimulating hormones in the mechanism of estrogen secretion. The reverse has been shown to be true for the secretory activity of the male gonad.

The possibility of preparing follicle-stimulating hormone extracts free from subminimal amounts of luteinizing hormones is discussed. Uterine and ovarian weights as a method of standardizing pituitary extracts is questioned, as the weight changes of the uterus and ovaries obtained with unfractionated extracts are not an index of the amounts of follicle-stimulating hormones and luteinizing hormones present but rather an expression of the relative proportions of the two.

CLAUDE J. EHRENBERG.

**Hoffmann, Fr.: Investigation of Formation of Female Ovarian Hormones in the Adrenal Cortex, *Zentralbl. f. Gynäk.* 64: 1075, 1940.**

Hoffmann studied the corpus luteum and follicle hormones of the adrenal cortex of female, male, and castrate male animals. The extract of the cortex was injected into castrated dogs, and the Robson modification of the Corner-Allen test was used. Extract of 250 Gm. of bovine adrenal cortex gave a maximal corpus luteum effect on the dog endometrium, characteristic of the sixth to eighth day of pseudopregnancy. Extract of 180 Gm. gave a 2-plus reaction; extract of 80 Gm. a positive or doubtful reaction. The reaction to the injection of steer adrenal cortex extract had half the corpus luteum effect compared with the bovine extract. Oxen showed a still weaker effect.

To determine follicle hormone effect, castrated mice were injected with the extract and amounts representing 30 Gm. of adrenal cortex were necessary to produce estrus effect equivalent to that of 1 I.U. of estrone. In comparison, 200 Gm. of adrenal gland and 100 Gm. of ovary are equivalent in producing the effect of 1 Corner unit. As the adrenal cortex is only 20 to 25 per cent of the mass of the gland, its relative corpus luteum potency appears to be higher. Hoffmann also found 1 unit estrone in 25 to 30 Gm. of adrenal cortex.

The author concludes that the adrenal cortex may be considered as accessory sexual glandular tissue whose pathologic significance lies in its ability to produce male and female sex hormones in great quantity in masculinizing and feminizing tumors.

R. J. WEISSMAN.

**Tscherne, E.: Contribution to the Etiology of Glandular (Endometrial) Hyperplasia, *Zentralbl. f. Gynäk.* 64: 1474, 1940.**

The author discusses briefly the theories of persistent follicle hormone and pituitary-midbrain effects in maintaining endometrial hyperplasia. In his opinion in these cases, the hypophysis has lost its ability to respond to the stimulus of peak circulating hormone with a response of producing the luteinizing prolan-B. In other words the difficulty is of central origin. The effect of large doses of follicle hormone in inhibiting the menorrhagia of these cases is a direct endo-

# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Endocrinology

Kosakae, Kanzaki, and Kusano: The Quantity of Sexual Hormone Discharged in the Urine of Pregnant Women After Castration, *Jap. J. Obst. & Gynec.* 23: 174, 1940.

In a patient whose both ovaries had been removed, the authors studied the amount of follicular and sexual hormone passed in the urine from six to nine days every month beginning with the sixth month of pregnancy. They continued these observations into the puerperium when daily observations were made. It was found that the results were identical with those observed in normal pregnant women. This is considered by them evidence that the follicular hormone is produced in the placenta.

J. P. GREENHILL.

Furuhjelm, M.: The Excretion of Estrogenic and Androgenic Substances in the Urine of Women, *Acta. obst. & gynec. Scandinav.* 20: 1, 1940.

The excretion of estrogenic and androgenic substances was determined in two-day lots of urine on 14 healthy women and on 10 women with myomas of the uterus. The curves of the 14 healthy women revealed a typical configuration. The excretion of estrogenic substances showed one, and occasionally two, pronounced peaks. A marked decrease in the estrogenic excretion occurred during menstruation. The estrogenic activity of the urine for two days varied between 20 I.U. and 400 I.U. of estrone. During the ovarian cycle, the healthy woman excretes estrogenic substances equivalent to 1,100 I.U. of estrone. In 10 out of these 14 patients, there was no decrease in the androgenic secretion during menstruation. There was a tendency to parallelism between the excretion of androgenic and estrogenic substance during the intermenstruum. Similar conditions were found in the curves of the 10 women with myomas.

The author also investigated 2 castrated women. He could find no estrogenic substance in the urine up to two weeks after castration. Androgenic substances were found in the same amounts after abortion as before and in approximately the same amounts in normal women.

J. P. GREENHILL.

Corner, George W.: The Rate of Secretion of Estrogenic Hormones by the Ovaries of the Monkey, *Macaca Rhesus*, *Bull. Johns Hopkins Hosp.* 67: 407, 1940.

The rate of secretion of estrogenic hormone by the ovaries of the young adult rhesus monkey (weighing 4 to 5 kilograms) is estimated tentatively as equivalent to about 200 International Units (20 gamma) of estrone daily.

Multiplying this figure by a factor of 15, to allow for the proportionate weight, the rate of production of estrogenic hormone by the ovaries of the human female

the former, administration of these principles will yield complete development; in the latter they are valueless. It is impossible to foretell whether the uterus will or will not respond to hormones.

Estrogen therapy for amenorrhea depends on the "estrin withdrawal hemorrhage" reaction. If it is not a true menstruation, the endometrium is in a nonsecretory phase. It is estimated that 25 to 30 mg. of estradiol benzoate are necessary to produce such bleeding. The effect is obtained only as long as treatment is continued unless the ovaries are capable of spontaneous function.

Rarely, if ever, will administration of hormones bring about premature termination of a normal pregnancy. Four milligrams of estradiol benzoate every eight hours for eight days are given for missed abortions. Quinine and pituitary induction are given on the fifth and eighth days if necessary. The author reports with this therapy 80 per cent of success in his cases.

That uterine inertia is a deficiency of estrogenic substance and may be overcome with hormone therapy is a supposition and without proof.

Estrogens stimulate development of breast glandular tissue and are of use in underdevelopment, but breasts will atrophy when stimulus is discontinued unless ovarian function is adequate. Chronic mastitis or involutionary mastitis is benefited by estrogenic therapy.

Estrogens do not cause secretion of milk; a prolactic function of the anterior pituitary is inhibited by estrogens. Large amounts of estradiol injected during the puerperium inhibit lactation and relieve breast engorgement.

So far no clinical evidence has shown that estrogens in ordinary dosages have brought about neoplastic changes. Most harmful effect of estrogenic therapy is depression of ovarian activity. A warning against prolonged treatment in young women is given.

Stilbestrol, a synthetic substitution, may be given orally as effectively as parenterally. One milligram of it is equivalent to 1 mg. of estradiol benzoate, and has proved of value in all of the above-mentioned conditions. The disadvantage is that it produces nausea and malaise when given in large doses.

FRED L. ADAIR AND JOHN R. KIGHT.

Scherf, David: *The Respiratory and the Circulatory System in Females With Ovarian Dysfunction*, *Ann. Int. Med.* 13: 1414, 1940.

Treatment with estrogenic hormones appears to have a beneficial effect upon disturbances in the respiratory and circulatory system of women at the menopause or under other conditions of ovarian hypofunction.

In 38 women, some of whom were being mistakenly treated for angina pectoris, myocarditis, or coronary sclerosis, the author was able to demonstrate changes in the electrocardiogram which might rightfully be ascribed to ovarian hypofunction, since they disappeared after administration of estrogenic hormone.

In every case, treatment with adequate dosages of estrogenic hormones was followed by very rapid relief of symptoms and the return of the electrocardiogram to normal. In some cases, the electrocardiographic changes vanished within eight days after the administration of as little as 1,000 to 2,000 International Units of estrogen daily. In other cases, the hypodermic injection of 10,000 to 50,000 units, two to three times a week for three to four weeks, was necessary for improvement.

The dyspnea of ovarian dysfunction, particularly at the menopause, occurs independently of effort and may be present when the patient is resting quietly.

The normal disturbances in respiratory and circulatory function at the time of the menopause may represent a most profound danger for women who already harbor an organic heart lesion. Such valvular lesions, or hypertension, quiescent for years, may suddenly produce decompensation when the middle forties are reached. The heart dilates quickly, and cardiac asthma, pulmonary edema, and peripheral congestion appear.

This event is not rare and it can be avoided. The estrogenic function of every cardiac patient should be continuously controlled, especially if the patient is at the age when disturbances of the menopause are likely to occur. Early prophylactic treatment with estrogenic hormones may save many lives.

J. P. GREENHILL.

metrial effect into which the hypophyseal mechanism does not enter as evidenced by the persistence of the hyperplasia. Several interesting cases are presented.

An 18-year-old girl had been treated in the past with corpus luteum, anterior pituitary, and eurette with varying success. Biopsy showed hyperplastic endometrium. Stilbestrol was given in 3 daily doses, 5, 10, and 15 mg., and the bleeding stopped after the third dose only to begin again eight days later, when biopsy again revealed the persistence of the hyperplasia.

A 47-year-old woman, bleeding fourteen days after a two months' amenorrhea, ceased flowing after a third daily dose of 100,000 I.U. of progynon B. Eight days later biopsy showed persistent hyperplastic endometrium.

A woman, 26 years old (menarche at 13, normal 28-day cycle), was shot in the head. Radiographs showed the slug lying directly behind the sella turcica. After two days of unconsciousness the patient slowly recovered but developed a Korsakoff's psychosis. Because of a homonymous hemianopia, descending optic atrophy, and mild facial paresis it was concluded that the projectile had passed in close proximity to the pituitary, causing a hematoma which had injured either the vegetative centers related to the pituitary or their hypophyseal connections. At any rate a 6-month period of amenorrhea followed the accident and the patient gained 22 kilograms. In a period of seven days 42,000 R.U. doses of prolan were given. Eleven days later a five-day flow occurred. No biopsy was done at this point. The author reconciles the result of this medication with Westmann's work on hypophysectomized animals who undergo follicular atrophy. Reactivation is possible by administration of chorionic hormone because this hormone in turn is activated by the gonadotropic hormone not affected by the operation. In the author's case menstruation was regularly produced at will eleven or twelve days after a series of doses of prolan. At the beginning of each of the menses of December and January, 1940, biopsies were done. In December glandular hyperplasia was found, i.e., pituitary midbrain connections were reestablished, but follicle hormone still blocked from affecting the midbrain. In January, thirteen months after the accident, a normal menstruating endometrium was found indicating restoration of central sensitivity to follicle hormone and ability of the midbrain to effect stimulation of luteinizing (prolan B) hormone.

R. J. WEISSMAN.

Jeffcoate, T. N. A.: Oestrogenic Hormone Therapy, *Brit. M. J.* 2: 671, 1939.

Estrogens, chemical substances that can promote estrus, in animals, can be obtained as estradiol, esterone, and estriol in human tissues and body fluids, believed to be produced as estradiol, which is secreted by the granulosa cells in the non-pregnant, and the placenta in pregnant females. Esterone and estradiol are more commonly used for therapeutic purposes as the benzoate or other esters dissolved in oil. Diethyl-stilbestrol (stilbestrol) is a synthetic product available for clinical use.

Diminished secretion of estradiol in the adult usually leads to menopausal symptoms, in youth, when the ovary has never functioned, to amenorrhea, oligomenorrhea, under-development of breasts and other sex characteristics. Endometrial biopsy shows atrophic endometrium and vaginal smears show fewer and smaller epithelial cells than normal.

Undoubtedly a large percentage of cases of menopausal symptoms can be eliminated by administration of estrogens. Dosage varies considerably, and is determined by trial. With symptoms controlled, smaller doses are needed. Gradual reduction is necessary.

Senile vaginitis and kraurosis vulvae may be cured with estrogens. In the former injection of 5 mg. twice weekly is recommended and the patient is usually symptom free in two to three weeks. Small doses should be continued for two or three months. Kraurosis vulvae requires more prolonged therapy. In gonococcal vaginitis, 0.1 mg. of esterone should be injected every one to two days and given orally 2 to 3 times daily.

Genital hypoplasia may be due to an estrogenic hormone deficiency or an inherent defect in the organ rendering it insensitive to hormone administration. In

larity between stilbestrol and the follicular hormones. Stilbestrol is particularly effective when taken by mouth. There is, however, no cancer-producing effect.

J. P. GREENHILL.

**Von Konrád, E.:** Treatment of Metropathia Hemorrhagica With Testosterone Propionate, *Zentralbl. f. Gynäk.* 64: 1135, 1940.

The author discusses his results in the treatment of metrorrhagia in 17 patients—the oldest 19 years of age. Five daily doses of 25 mg. testosterone were administered. All but two patients had ceased bleeding by the fifth injection. These two required 9 and 10 doses. Characteristically there followed varying periods of amenorrhea after which the patients again menstruated regularly. The favorable effect of the male hormone is attributed to its influence on luteinization. Von Konrád favors the routine use of male hormone in juvenile menorrhagia and in noncarcinomatous uterine bleeding of other etiology.

R. J. WEISSMAN.

**DeBarros, Rubins Monteiro:** Use of Testosterone Propionate in Hemorrhage Due to Myoma Uteri, *Rev. de gynec. e d' obst.* 1: 394, 1940.

The author reports a case of myoma uteri with severe hemorrhage in which he employed testosterone propionate in an effort to improve the patient's condition before operation. He feels that this substance can be utilized preoperatively with advantage to control the hemorrhage due to fibromyoma.

MARIO A. CASTALLO.

**Huber, Carl P., and Davis, M. Edward:** The Clinical Use of Gonadotropic Hormone From Pregnant Mares' Serum, *Surg., Gynec. & Obst.* 70: 996, 1940.

The administration of gonadotropic hormone from pregnant mares' serum has been followed by pregnancy in previously sterile patients in whom anovulatory menstrual cycles have been demonstrated.

This gonadotropic hormone has proved clinically effective in some cases of acyclic uterine bleeding associated with evidence of continued endometrial proliferation.

Amenorrhea resulting from inadequate ovarian activity has responded to this gonadotropic hormone by the occurrence of uterine bleeding.

No untoward effects have been demonstrated either locally or systemically following several hundred intramuscular and intravenous injections of this hormone.

Further carefully controlled clinical observations are necessary definitely to establish the therapeutic value and indications for the use of gonadotropic hormone from pregnant mares' serum.

WILLIAM C. HENSKE.

**Lawrence, Ch. H., and Moulyn, Adrian C.:** The Menopause: A Hormonic and Therapeutic Study, *New England J. Med.* 224: 845, 1941.

In only a small minority of women are the symptoms associated with "the change of life" sufficiently severe to compel them to consult a physician.

In their studies the authors found that a test for prolan was positive in only 48 of 100 women coming to the clinic for severe symptoms, in 81 per cent the symptoms being particularly those of vasomotor instability. Of these, 90 per cent were definitely benefited by adequate treatment with estrin. In the prolan negative group, however, estrin caused improvement in only 25 per cent, whereas simple psychotherapy or sedation brought relief in 80 per cent.

No relation was evident in either group between the presence or absence of estrin alone and the character or severity of symptoms. A predominance of vasomotor symptoms is suggestive of an overactive prolan production, but treatment with estrin should not be instituted until urinary assay proves that prolan is excreted.

If treatment with estrin is indicated, it should be given in effective amounts; the effective dosage, however, in any patient is an individual equation.

HUGO EHRENFEST.

Mazer, Charles, Israel, S. Leon, and Ravetz, Elkin: The Synthetic Estrogen Stilbestrol, J. A. M. A. 116: 675, 1941.

The authors review their experiences in 189 cases with stilbestrol. They feel that the biologic potency of stilbestrol when given hypodermically is five times greater than that of estrone and equal to that of estradiol benzoate. The ratio between the oral and the hypodermic doses of stilbestrol is 5 to 1 in the human being, as well as in the rat, in contrast to a ratio of 20 to 1 in terms of the rat unit for the natural estrogens. It is suggested that injections of adequate quantities of stilbestrol twice weekly is sufficient for clinical purposes.

One hundred and twenty-two patients receiving 0.2 to 5 mg. daily by the oral route or every fourth day parenterally showed complete relief in 68 per cent, partial relief in 27.9 per cent, and no relief in 4 per cent of the cases. Occasional cases of sporadic uterine bleeding were encountered as a result of the withdrawal of stilbestrol. In amenorrhea the authors gave 50,000 rat units in 5 divided doses in 15 women, and menstrual-like bleeding was produced in six of seven attempts. They were also successful in suppressing lactation by giving 3 to 10 mg. of stilbestrol daily for a period of from two to four days. Successful treatment in 50 per cent of the cases of migraine resulted from the use of stilbestrol. It was also effective in the treatment of juvenile vaginitis. Stilbestrol is also useful in reducing the insulin requirements of diabetics, but it has no effective place in the treatment of diabetes mellitus unless a corresponding menopausal syndrome is present.

The drug had to be discontinued in 22.2 per cent of the cases because of toxic symptoms, chief of which were nausea and vomiting, epigastric pain, and abdominal distress. The smaller the dose the less is the toxic effect. Tissue damage in the human being resulting from the administration of relatively large doses of stilbestrol given over a long period of time is not demonstrable by physical examination, and by ordinary laboratory means, although animals do show some kidney, liver, and adrenal gland changes.

WILLIAM BERMAN.

Weinstein, Weed, Collins, Lock, and Schlosser: The Effect of Diethyl Stilbestrol Dipropionate on Endometrial Transplants, *Endocrinology* 27: 903, 1940.

To determine the probability of successfully transplanting estrogenically primed endometrium and to study the effect of continued estrogenic administration on these transplants, the authors used diethyl stilbestrol dipropionate on adult virgin chinchilla rabbits. Two groups of animals, each of which except the controls received daily injections of 12,500 I.U. of stilbestrol until a total of 600,000 I.U. had been used, were laparotomized. Extreme hypertrophy of the uterine cornua, hypertrophy of the vagina, but no effect on the ovaries and oviducts were consistently noted. Portions of excised uterine cornua were sutured to the mesentery of the small bowel and the abdominal peritoneum. The animals were continued on the preoperative estrogen treatment, Group I receiving an additional dosage of 375,000 I.U., and Group II receiving an additional dosage of 525,000 I.U.

All transplants were successful with viable endometrial tissue. Cyst formation in the endometrium was constant even in the controls. The size of the cysts was in direct proportion to the amount of estrogen used as was vasodilatation, the only change demonstrable, in the surrounding host tissue. Microscopic examination of the transplant tissue revealed no invasive tendency or increased cellular activity, but because of the stimulating effect of the estrogen, the authors caution against the use of large doses of estrogens postoperatively, in women castrated to decrease symptoms of endometriosis.

CLAUDE J. EHRENBERG.

Joel, C. A.: The Question of the Stilbens, a Synthetic Follicular Hormone, *Monatsschr. f. Geburtsh. u. Gynäk.* 111: 63, 1940.

Stilbestrol which is cheaper than follicular hormones may replace the latter in the opinion of the author. Experimental research has proved a qualitative simi-

## Item

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### American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada, on Saturday, January 3, 1942, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination will proceed automatically to the Part II examination held in June, 1942.

Candidates for *reexamination* in Part I (written paper and submission of case histories) must request such reexamination by writing the Secretary's Office not later than November 15, 1941. Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their original examination.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Atlantic City, N. J., in June, 1942, immediately prior to the annual meeting of the American Medical Association.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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## Books Received

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ANALGESIA OBSTETRICA, el sueño crepuscular barbitúrico en el parto. By Juan Leon, Professor adjunto de Clínica Obstétrica de la Facultad de Ciencias Médicas de Buenos Aires, etc. 574 pages, 169 illustrations. El Ateneo, Buenos Aires, 1941.

DIE TÄGLICHE GYNAEKOLOGISCHE SPRECHSTUNDE. Von Dr. M. Rodecurt, Frauenarzt. 308 Seiten, 3 Abbildungen. Georg Thieme, Leipzig, 1941.

THE MARCH OF MEDICINE. New York Academy of Medicine Lectures to the Laity. 1940. Columbia University Press, New York, 1941.

ARCHIVOS DE LA CLINICA E INSTITUTO DE ENDOCRINOLOGIA. Director, Professor J. C. Mussio Fournier. Tomo I, Fasc. 1. and 2. (1937-1940) Imprenta "Rosgal." Montevideo, Calla Cerro Largo, 1941.

THE THERAPEUTICS OF INTERNAL DISEASES. Supervising editor: George Blumer, Clinical Professor of Medicine, Yale University School of Medicine, etc., Associate Editor: Albert J. Sullivan, Adjunct Clinical Professor of Medicine, George Washington and Georgetown Medical Schools, etc. Volume IV. 791 pages, and Volume V. 765 pages, both illustrated. D. Appleton-Century Co., New York, 1941.

Pattee, C. J., Venning, E. H., and Browne, J. S. L.: The Effect of Estrogens on the Pregnanediol Output During the Menstrual Cycle, *Endocrinology* 27: 721, 1940.

The effects on the menstrual rhythm of injections of estrogen, as recorded by other authors, are reviewed. Excretion of pregnanediol was studied in three women receiving estradiol benzoate (20,000 to 80,000 I.U.) during menstrual cycles. Decreased pregnanediol output was noted in all such cycles. The findings confirm the work of other authors, that, given in the luteal phase, estrogens will depress the urinary excretion of pregnanediol. The mechanism of the phenomenon is postulated.

CLAUDE J. EHRENBURG.

Herrnberger, K.: Oral Potency of Estradiol and Progesterone, *Zentralbl. f. Gynäk.* 65: 13, 1941.

The author administered estradiol in tablet form in doses up to 450 mg. without any observable proliferation effect on the endometrium of castrate women. In alcoholic solution, however, doses of 180 mg. estradiol were able to produce a proliferative phase in the endometrium. Herrnberger was unable to find any effect from large doses of oral progesterone. Pregninolone in oral dosage, however, was capable of producing a secretory phase in proliferated endometrium.

R. J. WEISSMAN.

Lawrence, Charles H., and Werthessen, Nicholas T.: The Endocrine Dyscrasia of Acne Vulgaris in Women, *Endocrinology* 27: 755, 1941.

The urinary androgen-estrogen ratios of eight normal women and eight women with acne were determined in forty-eight-hour specimens taken between the sixteenth and twentieth days of the menstrual cycle. The technique of the assay methods and the statistical and mathematical handling of the data are described in detail.

A significant increase in the ratio of androgens to estrogens measured as estrone equivalents, through abnormal lowering in estrogens was demonstrated in the acne group. This aberrant ratio is considered of more etiologic significance than the decrease of estrogen excretion alone. The findings from a clinical point of view are thought to agree with the biologic evidence concerning acne.

CLAUDE J. EHRENBURG.

Bauer, W.: Clinical Results of Follicle Hormone Therapy, *Zentralbl. f. Gynäk.* 64: 1682, 1940.

The author attributes the low incidence of failures in his own experience with follicle hormone therapy (12 in 374 cases), to his careful selection of cases. Juvenile metrorrhagia and polymenorrhea with hypermenorrhea responded with uniform good results. New uses for follicle hormone were found in treating fissured nipples and also urinary incontinence of young girls, although the rationale is not thoroughly understood.

R. J. WEISSMAN.

Miotti, Tito: Changes in the Genital Apparatus of the Female Guinea Pig Induced by the Action of Prostatic Extracts, *Ginecologia* 19: 141, 1941.

The author attempted to prove the presence or absence of hormonal activity in extracts of the prostate gland. Normal and castrate female guinea pigs were treated with these extracts.

The author concludes that there is no evidence of any hormonal effect of prostatic extracts upon the genital tract of the female guinea pig. In some instances there was observed slight vasodilatation among the smaller uterine veins.

CLAIR E. FOLSOME.



tested. Accordingly, a pregnant woman whose blood does not contain the Rh factor (Rh-, occurring in about 15 per cent of the general population) if married to an Rh husband (85 per cent in the random population), may produce anti-Rh agglutinins as a result of immunization with the Rh fetal blood. Should these agglutinins penetrate the placenta in suitable concentration they may serve as the source of the intrauterine hemolysis of fetal blood, the characteristic feature of erythroblastosis fetalis.<sup>4</sup>

The term iso-immunization denotes immunization within the same species, i.e., the individual being immunized and source of the antigenic (immunizing) stimulus belong to the same species. It is obvious that patients receiving repeated blood transfusions may be subjected to iso-immunization. A prerequisite condition is an antigenic difference in the bloods of recipient and donor. In each instance, this difference is expressed by the presence of a particular blood factor in the donor and its absence in the recipient. Although this condition is frequently satisfied in many cases of repeated transfusions, immune agglutinins are rarely produced because many human blood factors which immunize animals are not antigenic in man. An exception to this rule is the Rh factor which has recently been shown to be responsible for transfusion accidents in Rh- recipients who in the course of several transfusions produced anti-Rh agglutinins.<sup>5, 8, 9</sup> In short, the Rh factor is a good antigen for Rh- mothers as well as for Rh- recipients.

Iso-immunization in pregnancy as the cause of the production of atypical agglutinins responsible for an intra-group transfusion accident was suggested by Levine and Stetson<sup>1</sup> in 1939. In this case the patient (Group O), who harbored a dead fetus for two months, was transfused with her husband's blood (Group O) after the delivery of a macerated fetus (October, 1937). This transfusion was followed by an immediate severe reaction resulting in jaundice, anuria, and ultimate recovery. It was later shown that this patient's blood contained an atypical agglutinin which agglutinated about 80 per cent of Group O bloods. As was to have been expected, this agglutinin gradually diminished in titer and entirely disappeared from the blood at the end of one year. In 1940, or three years after the transfusion accident, it could be shown that the patient was Rh- and her husband Rh+. There is still further evidence that the atypical agglutinin in this patient was anti-Rh in its specificity since the same donors selected as compatible\* for subsequent uneventful transfusions in 1937 were later (1940) found to be Rh- in tests with a human anti-Rh serum.

Recent studies have shown that intra-group transfusion accidents previously reported in the literature<sup>5</sup> and additional cases recently observed by Levine, Katzin, and Burnham,<sup>2, 3, 10</sup> occurred frequently in conditions associated with pregnancy. It is characteristic of this group of cases that the accident occurs at the first transfusion. Accordingly, the immune agglutinin which must have been present prior to the transfusion but could not be demonstrated with the usual cross-matching procedure, was probably induced by the pregnancy.

\*These tests were carried out by Dr. E. M. Katzin.

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## Original Communications

### THE ROLE OF ISO-IMMUNIZATION IN THE PATHOGENESIS OF ERYTHROBLASTOSIS FETALIS\*

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**S**TUDIES on the cause of intra-group transfusion accidents associated with pregnancy have established the importance of the concept of iso-immunization of the mother by blood factors in the fetus transmitted from the father.<sup>1-5</sup> More recently it was found that the same theory of iso-immunization may serve as the basis for a theory on the pathogenesis of erythroblastosis fetalis, the well-described familial hemolytic disease of the newborn.<sup>3, 4, 6</sup>

The data to be presented indicate that erythroblastosis fetalis results from (1) iso-immunization of the mother by dominant hereditary blood factors in the fetus, as evidenced by the production of immune intra-group agglutinins and (2) the subsequent passage of these maternal agglutinins through the placenta and their continuous action on the susceptible fetal blood. In the great majority of the cases the blood factor involved has been shown to be either identical with or related to the Rh (Rhesus) agglutinogen first described by Landsteiner and Wiener with the aid of rabbit sera prepared by injection of Rhesus blood.<sup>7</sup> In other words, the rabbit anti-Rhesus immune sera and the sera of pregnant women suffering from intra-group transfusion accidents gave almost identical agglutination reactions on all human bloods

\*Aided by a grant from the Blood Betterment Association of New York City.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

TABLE I. OUTCOME OF 37 PREGNANCIES IN 7 PATIENTS

*(Modified After Levine, Katzin and Burnham<sup>3</sup>)*

Normal babies	10
Babies with erythroblastosis	7
Neonatal deaths	3
Stillbirths	5
Abortions or miscarriages (at least 6 spontaneous)	10
No data available	2

In 6 of these 7 women in whose blood atypical agglutinins were demonstrated, there were indications that the specificity of the antibodies corresponded to the anti-Rh. Obviously, the blood cells of these women did not contain the Rh factor and were therefore Rh-. These considerations suggested a statistical study of the bloods of women known to have given birth to infants in whom a diagnosis of erythroblastosis fetalis was established. If iso-immunization with the Rh factor plays a significant role in the pathogenesis of this disease, one should expect to find (1) a high incidence of Rh- reactions in this group of selected mothers and (2) a high incidence of anti-Rh agglutinins in their sera.

Whenever possible, the bloods of the fathers and the affected children were also tested, for, if the iso-immunization theory is correct, then 100 per cent of the fathers and the affected children in the series of Rh-mothers should be Rh+.

In each case, suspensions of red blood cells were tested with potent human anti-Rh agglutinins to determine whether the blood was Rh- or Rh+. Since the Rh factor is a constant immutable hereditary property of the red blood cells, it is obvious that such tests could be made at any interval after the last delivery of an affected infant.

The presence or absence of atypical agglutinins was determined by testing each serum with blood suspensions of at least 10 individuals of Group O, of which at least 1 was Rh-. It is obvious that the possibility of demonstrating atypical agglutinins was better if the serum was studied soon after birth of the affected infant.

#### EXPERIMENTAL

*Selection of the Cases.*—This study is based chiefly on blood tests of 153 mothers who delivered one or more infants suffering from one of three clinical forms of erythroblastosis fetalis, i.e., fetal hydrops, icterus gravis, or anemia of the newborn. Of these, 115 were under observation either by one of the authors or by other collaborators.\* Thirty-eight mothers were referred to us from several sources mainly outside of the metropolitan area of New York. The diagnosis in the affected infants in the latter group could be accepted on the basis of a history submitted by the physicians referring the case. In each case, some or all characteristic features were present, such as a significant obstetrical history of previous miscarriages or stillbirths, or infants with erythroblastosis fetalis—and the accepted diagnostic criteria such as severe icterus at or shortly after birth, enlarged liver and spleen, excess of normoblasts

\*Drs. L. Goldman, C. Javert, S. Polayes, and H. Schwartz.

The atypical agglutinins in some of these cases were shown to have the unusual property of greater activity at 37° C. than at 20° C. (low room temperature). For this reason, the term "warm agglutinins" was applied to these antibodies.<sup>10</sup> This observation offers a possible explanation for the frequent failure of the cross-matching tests to detect this form of intra-group incompatibility. It is therefore recommended that in performing the compatibility test, the patient's serum and donor's blood cell suspension be incubated at 37° C. for thirty minutes before the mixture is centrifuged (one minute at 500 r.p.m.) for sedimentation and subsequent resuspension.<sup>4, 11, 12</sup>

The relationship of iso-immunization and certain pathologic states in the pregnant woman or in the fetus was pointed out by Levine and Katzin.<sup>2</sup> In an analysis of 12 intra-group transfusion accidents associated with pregnancy in which atypical agglutinins were demonstrated, these authors observed a high incidence of toxemia, spontaneous abortions and miscarriages, and stillbirths in the past obstetric histories. Accordingly, it was assumed that "there does appear to be a correlation of the complications with the incidence of atypical agglutinins, and one can speculate as to their relationship."

This observation made it possible to enlarge the source of the material to be studied instead of limiting it to the comparatively rare transfusion accidents in pregnancy.

Shortly thereafter, one of us (L. B.) observed a patient who suffered from a severe transfusion accident following the delivery of an infant in whom a diagnosis of erythroblastosis fetalis was established. The obstetric history in this case (R. C.)<sup>\*</sup> and in still another case (J. L.) not transfused, were so striking as to suggest a theoretical basis for the pathogenesis of erythroblastosis fetalis.<sup>3, 4</sup> One of these mothers (R. C.) had three pregnancies, the first and third of which resulted in infants with erythroblastosis fetalis and the second pregnancy terminated in a macerated fetus. In the other case (J. L.), there had been 10 pregnancies, the first of which resulted in a normal infant; there were 3 spontaneous abortions and the remaining 6 pregnancies resulted in infants who survived one to three days. In at least 3 of these neonatal deaths there was sufficient evidence to support a diagnosis of erythroblastosis fetalis. This woman's blood was tested in the eighth month of her eleventh pregnancy. Since atypical agglutinins were already present, it was anticipated that the baby to be born would be affected. Actually, the infant suffered from anemia of the newborn, one of the several manifestations of erythroblastosis fetalis.

The two cases mentioned were among the seven patients with 37 pregnancies which formed the basis for the preliminary observation that the pathogenesis of erythroblastosis fetalis depends on iso-immunization of the mother by the fetus. The findings in these 37 pregnancies are reproduced in Table I.

<sup>\*</sup>Another patient of Dr. Burnham (G. B.) who died from a transfusion anuria following the delivery of an infant with fetal hydrops, was mentioned in previous papers.<sup>2, 3, 10</sup> These two cases were the first to show the relationship of intra-group transfusion accidents and erythroblastosis fetalis. A more detailed discussion is given in a paper by Burnham.<sup>13</sup>

2. *E. B. (Group AB)*: A patient of Dr. Freed had two full-term pregnancies. The first infant was very pale at birth and survived but one and one-half hours. No other data were available. The second infant, born April, 1941, showed classical symptoms of congenital anemia.

3. *M. S. (Group O)*: A patient of Dr. Paul delivered a normal infant in 1931; this pregnancy was followed by a long interval of sterility. The second pregnancy (April, 1941) resulted in an infant suffering from icterus gravis.

*Specificities of the Anti-Rh sera, M. F., E. B., and M. S.*—A complicating feature in the behavior of the human anti-Rh sera is their failure to give entirely parallel reactions when tested with numerous bloods.<sup>14, 17</sup> Thus these sera give varying incidences of Rh- reactions (Table II).

TABLE II. RESULTS OF PARALLEL TESTS ON 334 RANDOM BLOODS OF ALL GROUPS

ANTI-Rh SERUM FROM PATIENT	PER CENT	
	Rh+	Rh-
E. B.	87	13
M. F.	85	15
M. S.	73	27

The greater incidence of Rh- reactions with serum M. S. is manifested by the fact that some bloods diagnosed as Rh+ in their reactions with sera E. B. or M. F. are not agglutinated by serum M. S.\* This fact is applicable to the bloods of only 3 of the 29 mothers which were tested with each of the three sera.

These serologic observations which are of more than academic interest, will be published in detail elsewhere, but reference will be made later (page 932) to the significance of these findings in connection with the iso-immunization by the fetus.

*Statistical Data on the Rh Blood Factor in 153 Mothers of Infants with Erythroblastosis Fetalis.*—This study reveals an incidence of about 90 per cent Rh- reactions in contrast to 15 per cent Rh- reactions in the random population. The actual analysis is rendered somewhat complex because not all bloods were tested with each of the three anti-Rh sera (Table III).

TABLE III

ANTI-Rh SERUM	NUMBER OF MOTHERS' BLOODS TESTED	PER CENT	
		Rh+	Rh-
M. F.	142	10	90
E. B.	60	15	85
M. S.	28	7	93
Combined results	153	7	93

The higher incidence of Rh+ with serum E. B. is due to the fact that more mothers Rh+ with serum M. F. were tested with serum E. B. than with serum M. S. At least one of the bloods Rh+ with serum E. B. can be considered Rh-, because this blood contains very active anti-Rh agglutinins.

\*Very rarely, the converse specific effect is obtained, i.e., blood Rh- with serum M. F. is Rh+ with serum E. B. or M. S.

in the peripheral circulation, progressive anemia, and in fatal cases post-mortem findings of extramedullary hematopoiesis.

In addition to the 153 mothers of infants in whom a diagnosis of erythroblastosis fetalis was established, data will be presented below (p. 933) in a smaller number of women whose pregnancies terminated in habitual abortion, miscarriages, stillbirths, or macerated fetuses.

*Technique of the Agglutination Tests.—Diagnosis of Rh+ and Rh- blood:* One or more drops of anti-Rh serum are mixed in small test tubes (75 × 10 mm.) with 2 drops of a washed 1 per cent to 2 per cent cell suspension (this corresponds to a suspension made by adding one drop of whole blood to 4 c.c. saline). The cell suspension is preferably prepared from the clot.

The tubes are shaken and incubated in a water-bath at 37° C. for one hour, at the end of which period each tube is properly identified and all tubes are centrifuged at low speed (500 r.p.m.) for one minute. After replacing the tubes in the rack, the sedimented cells are resuspended by gentle shaking and readings are recorded. Those mixtures in which no gross agglutination is visible are examined microscopically (low magnification) by withdrawing with the aid of a glass rod some of the mixture onto a slide. Bloods showing no agglutination are Rh-.

*Detection of Anti-Rh in Human Sera.*—Two drops of the serum to be tested are added to each of 10 small test tubes and each tube receives two drops of washed cell suspension of ten different Group O bloods. As a rule, at least one Rh- blood is included. The tests are incubated at 37° C. for one hour, and readings are made after centrifuging the tests and resuspension of the sediments as indicated above.

All cases were tested with one or more of three potent anti-Rh sera. Since the first serum employed (December, 1940) was of Group A (patient M. F.) all bloods of Groups O and A could be tested directly. In order to test bloods of Groups B and AB, it was necessary to treat this serum with an Rh- blood of Group B, in order to remove the normal iso-agglutinin anti-B. In April, 1941, the second potent anti-Rh serum was found (Patient E. B.). Since this serum belonged to Group AB, it could be used directly on bloods of all groups. In May, 1941, the third anti-Rh serum (M. S.) of Group O became available.

In the latter part of these studies, bloods of all groups could be tested in parallel with three anti-Rh sera. This became possible because of the availability of Witebsky's group specific soluble Substances A and B,<sup>15\*</sup> the addition of which in small quantities inhibited the action of agglutinin anti-A and anti-B without affecting the activity of anti-Rh.

In any event, each of the three sera gave distinct agglutination reactions so that there was never any doubt as to the diagnosis of Rh+ or Rh-, in any blood tested with a particular serum.

A brief obstetric history of these patients is given below:

1. *M. F. (Group A):* A patient of Dr. P. Vogel had 7 pregnancies of which 6 were full term and one terminated at six months. A diagnosis of erythroblastosis fetalis was made in the last two infants, the most recent one in December, 1940. Serum obtained several weeks post-partum contained potent anti-Rh agglutinins. The agglutinins remained very active though they were somewhat weaker in the blood specimen drawn in May, 1941.

\*Supplied by courtesy of Eli Lilly & Co.

It is of great interest that the anti-Rh agglutinins may be demonstrable for such unusually long periods, as two years post partum. Probably the long duration indicates an intense degree of iso-immunization which may perhaps influence the outcome of the next pregnancy with an Rh+ fetus. More specifically, reference is made to the clinical observation on the high incidence of spontaneous abortions and miscarriages in mothers of infants with erythroblastosis fetalis (p. 933).<sup>3, 18, 19</sup>

The results shown in Tables III, IV, and V indicate that a combination of Rh- mother, Rh+ father, and affected infant can be used as a laboratory test to support a diagnosis of erythroblastosis fetalis. Such results which are present in about 90 per cent of the cases should be of value in the diagnosis of mild, atypical, or borderline cases of this condition.

*The 11 Cases in Which Iso-immunization with Rh is Excluded.*—When these exceptional cases were first observed, it was assumed that blood factors other than Rh may also induce iso-immunization. This explanation seemed plausible since Levine and Polayes<sup>20</sup> had already demonstrated a new blood factor by means of an atypical hemolysin found to be the cause of a post-partum transfusion reaction.\* Indeed, this antibody seemed to differentiate the bloods of several of the Rh+ mothers from those of their husbands or affected children in a manner compatible with the concept of iso-immunization. However, the results were only suggestive and further study was hampered by the weak activity of the antibody.

More decisive results, however, were obtained with the reactions of an atypical agglutinin found in the serum of one of the 11 Rh+ mothers (patient K. F.).<sup>21</sup> This patient of Dr. Javert had one full-term, normal pregnancy; one infant with erythroblastosis fetalis (1937) and a missed abortion. When tested she was again several months pregnant. The antibody in this serum gives strong reactions almost exclusively on bloods which are Rh- with serum M. S. Accordingly, the blood factor identified by this atypical agglutinin must have some genetic relationship with Rh. Since this serum became available late in the course of this study, the bloods of the remaining mothers of this group must be retested with this new agglutinin.

Reference again is made (p. 931) to the bloods of 3 mothers of erythroblastic babies which were Rh+ with two anti-Rh sera but Rh- with the third serum M. S. These cases were included in the Rh- series because in one instance the husband and in the other the affected child were Rh+ with each of the three anti-Rh sera.

*The Theory of Heterospecific Pregnancy.—The Distribution of Blood Factors A, B, and Rh in Red Blood Cells, Tissue Cells, and Body Fluids.*—It is of interest that a difference in the blood groups of mother and infant was the basis of an older theory on the pathogenesis of familial icterus gravis.<sup>†22, 23</sup> In the literature, this concept has been referred to as "heterospecific pregnancy." The theory, since abandoned

\*This mother had 4 miscarriages and 8 full-term, presumably normal infants.

†At that time (1923) the more comprehensive term, erythroblastosis fetalis, was not yet in use.

Three mothers whose blood was Rh+ with serum M. F. or E. B. were Rh- with serum M. S. These three cases listed as Rh- could be considered as instances in which iso-immunization could occur, because in two instances the husband's blood, and in the third the affected child's blood were Rh+ with each of the three sera.

The striking difference in the incidence of the Rh factor in the selected population of mothers with erythroblastic babies and in the random population strongly supports the concept of iso-immunization. Since the incidence of Rh- bloods is very high in these mothers, it could be anticipated on the basis of the iso-immunization theory that the affected infants and the fathers in the series of Rh- mothers are exclusively Rh+. As will be shown such results were obtained in tests on 89 fathers and on 76 infants in whom a diagnosis of erythroblastosis fetalis was made (Table IV).

TABLE IV. INCIDENCE OF RH+ AND RH- IN HUSBANDS AND AFFECTED INFANTS OF THE 141 RH- MOTHERS

	NUMBER TESTED	Rh+	Rh-	EXPECTANCY OF Rh- IN RANDOM POPULATION
Husbands	89	89	0	13 (89 × 15%)
Affected infants	76	76	0	11 (76 × 15%)

The findings in this table are based on tests with serum M. F. which gives an incidence of 15% Rh- reactions.

The findings in Tables III and IV strongly indicate the iso-immunization of the Rh- mother by the Rh factor in fetal blood. The final proof for such iso-immunization can be supplied only by the demonstration of anti-Rh agglutinins in the mother's blood. Obviously, the likelihood of finding such agglutinins will be greater if the mother's blood is tested soon after the delivery of an infant suffering from erythroblastosis fetalis. This is borne out by the findings presented in Table V.

TABLE V. INCIDENCE OF ANTI-RH AGGLUTININS IN 141 RH- MOTHERS

INTERVAL AFTER LAST DELIVERY OF AN AFFECTED INFANT	AGGLUTININS PRESENT	AGGLUTININS NOT FOUND
2 months post partum	33	37
2 months to 1 year past partum	5	15
1 year or longer post partum	2	39
During next pregnancy	2	5
No data	0	3
Total	42	99

The failure to detect anti-Rh agglutinins in many cases tested shortly after the delivery of an affected infant does not exclude their presence at some previous period during the course of their pregnancy. Since the course of antibody production in general is characterized by a gradual rise, a period of maximum activity, and gradual disappearance, it is conceivable that in some cases anti-Rh agglutinins, after exerting their lytic effect on the fetus, rapidly disappeared from the blood so that none could be demonstrated at the time of delivery. It is therefore indicated that the bloods of mothers known to have delivered babies with erythroblastosis fetalis be studied at several intervals during course of future pregnancies. Furthermore, it is conceivable that antibodies capable of reacting in vivo cannot be demonstrated because of limitations in the sensitivity of the technique employed.



glutinins were observed. Three of these patients suffered from intra-group transfusion accidents following an abortion or stillbirths.

Two of these 5 patients had just delivered presumably normal infants in spite of the presence of moderately active anti-Rh agglutinins. Unfortunately, hematologic and other clinical data were not obtained so that a mild form of erythroblastosis fetalis could not be entirely excluded. However, the obstetric histories reveal that one of these patients (H. H.) had three consecutive miscarriages and the other (L. L.) had two miscarriages and one premature infant who survived for ten days.

The association of intragroup transfusion accidents, in the presence of atypical agglutinins, in three patients following an abortion, a miscarriage, and a stillbirth, respectively, was observed by us in the analysis of reports by Parr and Krischner,<sup>29</sup> Johnson,<sup>30</sup> and Zacho.<sup>31</sup> Other instances of intragroup transfusion accidents following abortions, miscarriages, or stillbirths, in the absence of atypical agglutinins have been reported by several authors.<sup>32, 33</sup> Very probably the transfusion accidents reported in the five papers quoted are ultimately attributable to iso-immunization by the fetus.

In any event, it is the action of maternal immune agglutinins on the fetus which may cause its death at any stage of its development so that the same mechanism may be responsible for erythroblastosis fetalis in the surviving infant as well as some cases of habitual abortion.

#### DISCUSSION

The numerous theories on the pathogenesis of erythroblastosis fetalis were recently reviewed by Darrow<sup>19</sup> who, in a hypothetical discussion, anticipated the iso-immunization theory. This author suggested an antigen-antibody reaction based on differences in maternal and fetal hemoglobin or other constituents of red blood cells as the most plausible explanation. A similar view was previously mentioned by Ottenberg,<sup>23</sup> but neither author presented experimental data to support their theses.

The findings presented establish the significant role of iso-immunization of the mother by blood factors in the fetus in the pathogenesis of erythroblastosis fetalis. Of prime importance is the Rh factor in the fetal blood which is transmitted as a dominant mendelian gene from the father.<sup>14</sup> Statistical evidence was offered to prove that its presence in the blood of the father and affected infant is a prerequisite condition for the iso-immunization of the Rh- mother. But in the final analysis, the proof of iso-immunization by the Rh factor was the demonstration in many instances of anti-Rh agglutinins in the mother's blood. It is the continuous intrauterine action of anti-Rh agglutinins with the Rh positive fetal blood over a period varying from weeks to months which causes a progressive hemolysis of fetal blood.

The reaction of anti-Rh antibody and Rh blood takes the form of agglutination in the test tube but in the fetal circulation the end result is hemolysis. Attempts to demonstrate corresponding hemolytic reaction in the test tube by the addition of fresh human serum have so far failed.

for lack of evidence, does not differ in principle from the iso-immunization theory in which the Rh factor plays such a prominent role. According to the concept of heterospecific pregnancy, given a mother of Group O and an infant of Group A (or Group B), the maternal anti-A (or anti-B) agglutinins are theoretically capable of acting on the Group A (or Group B) fetal blood. Actually, there is now evidence that in the example cited the mother's normal iso-agglutinin anti-A (or anti-B) is increased in titer as a result of iso-immunization with the A (or B) blood of the fetus.<sup>24, 25</sup> Nevertheless, the maternal agglutinins are specifically inhibited from acting on the fetal blood because of the wide distribution of the A and B factors in tissues and body fluids.

However, this applies to about 80 per cent of all individuals (secretors)<sup>26</sup> and if a fetus of Group A belongs to the class of non-secretors (20 per cent), it is conceivable that the maternal iso-agglutinin anti-A may serve as the source of the intrauterine hemolytic process. Accordingly, the older theory of heterospecific pregnancy may have to be invoked at least for selected cases of erythroblastosis fetalis in which the Rh or other blood factors fail to indicate iso-immunization by the fetus.

From these considerations on heterospecific pregnancy and in view of the established importance of the Rh factor in the pathogenesis of erythroblastosis fetalis, it can be assumed that the Rh factor is probably not present in tissue cells or body fluids, but rather is limited to red blood cells only. Otherwise, the maternal anti-Rh agglutinins would be specifically inactivated and therefore incapable of inducing the hemolytic action on the Rh+ fetal blood. Tests made by Levine and Katzin<sup>27</sup> with numerous specimens of saliva, a few specimens of sperm cells, and seminal fluid, indicate that the Rh factor is not present in the material tested.\*

*Iso-immunization in Habitual Abortion and Stillbirth.*—Reports from the literature indicate that the obstetric history of mothers of infants with erythroblastosis fetalis reveals a high incidence of abortions, miscarriages, and stillbirths. Macklin<sup>18</sup> and Darrow<sup>19</sup> stated that the mechanism responsible for the pathogenesis of erythroblastosis fetalis applies also for these abortions and stillbirths. This view is supported by the results in the present study. That iso-immunization by the fetus and subsequent action of maternal agglutinins on fetal blood may be the mechanism of these abortions and stillbirths is indicated in the data presented in Table I.<sup>3, 4</sup>

Another group of women were investigated because of their history of habitual abortion and stillbirths, but these women had no infants with erythroblastosis fetalis. Many of these women were Rh- but a satisfactory statistical analysis similar to the study on erythroblastosis fetalis is more difficult because habitual abortions and stillbirths may be manifestations of many conditions. Nevertheless, there is sufficient evidence in at least five† cases of this group to include them with the mothers of erythroblastic infants, because iso-immunization by the Rh factor in the fetus could be demonstrated. In each of these cases, anti-Rh ag-

\*Similar observations on saliva were recently reported by Wiener and Forer.<sup>28</sup>

†Four of these patients were discussed in our previous papers.<sup>1-3</sup>

nancy with an Rh+ fetus may be required before a sufficient degree of iso-immunization is attained.

It has been recorded by Javert<sup>37</sup> that erythroblastosis fetalis in one of its several forms, occurs once in 400 deliveries, but it is probable that this condition has a still higher frequency, especially if some cases of habitual abortion and stillbirths are manifestations of iso-immunization. Actually, the incidence of matings in which iso-immunization with Rh may occur (Rh+ husband and Rh- wife) is 85 by 15 or 13 per cent of all matings. Consequently, one would expect a much higher incidence of erythroblastosis fetalis. There are, however, a number of factors tending to reduce this incidence, such as, for example, the current tendency to small families and the inability of many Rh- women to respond to iso-immunization.

The data on erythroblastosis fetalis and the recent studies on the iso-immunization with the blood factors A and B in the absence of any pathologic conditions in the mother or the infant indicates that immunizing substances derived from the fetus make their way through the placental barrier into the maternal circulation. Since the Rh factor, in contrast to the A and B substances, is probably limited to only red blood cells, it is assumed that fetal blood in one form or another penetrates the villus in sufficient quantity to induce immunization in the mother.

#### SUMMARY AND CONCLUSIONS

1. In 93 per cent of the cases investigated, erythroblastosis fetalis results from the iso-immunization of the Rh- mother by the Rh factor in the red blood cells of the fetus.

2. In the remaining cases, blood factors other than Rh are responsible for the iso-immunization.

3. Agglutination tests for the Rh factor are of value as a laboratory aid in the diagnosis of erythroblastosis fetalis.

4. The pathologic manifestations of this disease are produced by the intrauterine action of maternal immune agglutinins on the susceptible red blood cells of the fetus.

5. It is probable that iso-immunization is also the cause of a certain proportion of habitual abortions and stillbirths.

6. Intra-group transfusion accidents associated with pregnancy can now be prevented by the use of Rh- donors and by means of modified cross-matching test.

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#### REFERENCES

- (1) *Levine, Ph., and Stetson, R.*: J. A. M. A. 113: 126, 1939. (2) *Levine, Ph., and Katzin, E. M.*: Proc. Soc. Exper. Biol. & Med. 45: 343, 1940. (3) *Levine, Ph., Katzin, E. M., and Burnham, L.*: J. A. M. A. 116: 825, 1941. (4) *Levine, Ph.*: AM. J. OBST. & GYNEC. 42: 165, 1941. (5) *Wiener, A. S., and Peters, H. R.*: Ann. Int. Med. 13: 2306, 1940. (6) *Levine, Ph., Vogel, P., Katzin, E. M., and Burnham, L.*: Science 94: 371, 1941. (7) *Landsteiner, K., and Wiener, A. S.*: Proc. Soc. Exper. Biol. & Med. 43: 223, 1940. (8) *Levine, P., Katzin, E. M., Vogel, P., and Burnham, L.*: Symposium of the American Human Serum Association, June 2, 1941, Cleveland.

One of the most striking features of erythroblastosis fetalis is the wide variety of clinical syndromes it embraces, such as, the extremely fatal form of fetal hydrops and the mild, frequently unrecognizable anemias of the newborn.<sup>34</sup> These clinical forms are probably the result of varying degrees and duration of iso-immunization during the course of the pregnancy. Nothing is as yet known concerning the exact time and conditions during the course of the pregnancy when iso-immunization begins. If some cases of habitual abortions are a manifestation of iso-immunization, then the process may start shortly after conception occurs. At any rate, it is conceivable that the prolonged action of immune iso-agglutinins on the susceptible fetal blood may induce more severe damage than the action of agglutinins produced very late in the course of a pregnancy.

The clinical observation has been made that some infants may be born apparently free from the condition, but in the course of a few days, severe anemia and jaundice make their appearance. It is difficult to correlate this fact with the iso-immunization theory since the infant after birth should be free from any further action by the maternal agglutinins. The source of the delayed hemolysis has been suspected to be the colostrum, but in a number of these cases the infant was not breast fed. An alternative explanation is the storage of mother's agglutinins by the tissue of the fetus so that their subsequent release may then induce the hemolysis several days after birth.

A few practical applications based on these studies are of importance to the obstetrician. In the first place the data presented make it clear why caution must be exercised in selecting compatible donors for transfusing mothers of infants with erythroblastosis fetalis or those with a history of habitual abortions, a stillbirth, or a neonatal death. It is of interest that 8 of the 141 Rh- mothers suffered from severe intra-group transfusion reactions. Such accidents can be prevented if Rh-donors are available for Rh- mothers<sup>3</sup> and if the modified compatibility (cross-matching) test be employed for the detection of the "warm" anti-Rh agglutinins (p. 927).<sup>4, 11, 12</sup>

Furthermore, there are indications from a small number of cases that the affected infant maintains higher levels of hemoglobin and red blood cell counts if he is transfused with Rh- blood instead of Rh+ blood. The rationale for this suggestion is drawn from the fact that the infant's own Rh+ blood is undergoing destruction.<sup>35</sup>

The hereditary nature of erythroblastosis fetalis, hitherto unknown, can now be stated in terms of the iso-immunization theory. In some families, every pregnancy but perhaps the first, terminates in either an abortion, a stillbirth, or an infant with erythroblastosis fetalis; while in other families, only one of several pregnancies results in an affected infant. Since the Rh factor is inherited as a simple mendelian dominant,<sup>14</sup> it is obvious from a genetic standpoint, that this striking difference in familial incidence of the disease is determined by the homozygosity (RhRh) or heterozygosity (Rh rh) of the father's blood.<sup>36</sup> The genetic details and evidence supporting this concept will be given elsewhere. It is, however, appropriate to state at this point, that the first born is frequently but not always spared because more than one preg-

invariably showed a true conjugate of average length. It seems reasonable, therefore, to postulate that the occipitoposterior position is caused, in the main, by adaptation of the head to an inlet possessing a narrow fore pelvis and an ample anteroposterior diameter. In this way, the larger occipital part of the fetal head avoids the narrowest segment of the pelvic brim. The pelvic type which comes nearest to these specifications is the anthropoid variety, and consequently it is found that these forms largely account for most of the primary posteriors. However, a gynecoid type with a narrow fore pelvis or an android-anthropoid type may favor this position, for both satisfy the pelvic architectural requirements mentioned.

An attempt was made to ascertain, if possible, why a primary occipitoposterior position occurred in the remaining 17 per cent (34 cases) that did not show a narrowing of the fore pelvis. Of these, it may be said that in 10 cases the pelvis was so large or the baby so small in relation to the pelvis that the factors which ordinarily make it necessary for adjustment of the head to the optimum inlet diameters did not come into play, and the occipitoposterior position could be largely ascribed to a matter of chance. The same may be said of an additional 4 cases in which the inlet was so symmetrically round that no particular position was favored and chance may have played a similar role. At least 90 per cent of the primary posterior positions, therefore, may be accounted for on the basis of the variations in the pelvic architecture at the pelvic inlet.

The secondary occipitoposterior positions, that is, those cases which engaged in some position other than the occipitoposterior and rotated to the posterior lower in the pelvis, represent variations of the internal rotation mechanism and will be considered later under that heading.

Another point that should be mentioned here deals with variations in degrees of occipitoposterior positions. Ordinarily when we speak of the vertex in the R.O.P. position we infer that the sagittal suture occupies the right oblique diameter of the inlet. This is not entirely true in all cases. Actually it is noted that the sagittal suture may occupy a number of intervening oblique axes so that some posterior positions engage with the occiput just slightly posterior to true transverse while others engage in the generally accepted oblique diameter of the brim and still others engage almost directly posterior. The pelvis plays an all important role in determining the degree to which the occiput is posterior for, it is noted, that the more narrow the brim the more posterior is the occiput. The practical significance of these variations in the degree to which the occiput is posterior is related to the mechanism of descent, because in the true primary posteriors, as we may designate those posteriors in which the occiput is at or behind the sacroiliac synchondrosis, the fetal back practically overlies the mother's spine and, as will be shown later, the axis of fetal drive is not as favorable as when the occiput and back are more anterior.

If it is true then that the occipitoposterior position represents correct adaptation of the fetal head to the shape of the brim, we should not consider it a malposition but rather as the optimum position for

- (9) Wiener, A. S.: Arch. Path. 32: 227, 1941. (10) Levine, P., Katzin, E. M., and Burnham, L.: Proc. Soc. Exper. Biol. & Med. 45: 346, 1940. (11) Levine, P., Katzin, E. M., and Vogel, P.: In preparation. (12) Levine, P.: Cited by Wiener.<sup>9</sup> (13) Burnham, L.: AM. J. OBST. & GYNEC. 42: 389, 1941. (14) Landsteiner, K., and Wiener, A. S.: J. Exper. Med. 74: 309, 1941. (15) Witebsky, E., Klendshoj, N. C., and Swanson, P.: J. A. M. A. 116: 2654, 1941. (16) Levine, Ph.: Unpublished observations. (17) Levine, Ph., and Katzin, E. M.: Unpublished observations. (18) Macklin, M. T.: Am. J. Dis. Child. 53: 1245, 1937. (19) Darrow, E. R.: Arch. Path. 25: 378, 1938. (20) Levine, Ph., and Polayes, S. H.: Ann. Int. Med. 14: 1903, 1941. (21) Levine, Ph., Javert, C., and Katzin, E. M.: In preparation. (22) Hirsfeld, L.: Konstitutionserologie und Blutgruppenforschung, 1928, Berlin, Julius Springer. (23) Ottenberg, R.: J. A. M. A. 81: 295, 1923. (24) Jonsson, B.: Acta path. et Microbiol. Scandinav. 13: 424, 1936. (25) Levine, Ph.: Unpublished data. (26) Schiff, F., and Sasaki, H.: Ztschr. f. Immunitätsforsch. u. exper. Therap. 77: 129, 1932. (27) Levine, Ph., and Katzin, E. M.: Proc. Soc. Exper. Biol. & Med. (In press.) (28) Wiener, A. S., and Forer, S.: Proc. Soc. Exper. Biol. & Med. 47: 215, 1941. (29) Parr, E. L., and Krischner, H.: J. A. M. A. 98: 47, 1932. (30) Johnson, R. A., and Conway, J. F.: AM. J. OBST. & GYNEC. 26: 255, 1936. (31) Zacho, A.: Ztschr. f. Rassenphysiol. 8: 1, 1936. (32) Goldring, W., and Graef, I.: Arch. Int. Med. 58: 825, 1936. (33) Bernstein, A.: AM. J. OBST. & GYNEC. 39: 1045, 1940. (34) Diamond, L. K., Blackfan, K. D., and Baty, J. M.: J. Pediat. 1: 269, 1932. (35) Katzin, E. M., Vogel, P., and Levine, P.: Unpublished data. (36) Levine, Ph.: In preparation. (37) Javert, C.: AM. J. OBST. & GYNEC. 34: 1042, 1937.

## THE OCCIPITOPOSTERIOR POSITION\*

### ITS MECHANISM AND TREATMENT

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THE problems presented by the occipitoposterior position have been the subject of many studies and much controversy. My only apology for reconsidering this subject arises from the fact that at the Sloane Hospital for Women we have been studying the pelvis and the correlated mechanisms of labor with the aid of the x-ray in a large number of cases of all types. Among these a random selection of 100 occipitoposteriors that terminated in easy spontaneous or low forceps deliveries and an equal number of midpelvic arrests provided two contrasting groups for study. The data obtained in the course of a careful study of these cases is the basis for the present report.

### ETIOLOGY

A close relationship of the shape of the pelvic brim to the engaging position of the vertex has been shown previously by Thoms and in several communications from the Sloane Hospital. It has been stated that the anthropoid pelvis favors the posterior position. One of the most striking observations in this series was the high incidence (83 per cent) of some degree of narrowing of the fore pelvis in pelvis associated with a primary occipitoposterior position. In addition to the narrowing of the fore pelvis, it was noted that the pelvis almost

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cases when contrasted to those which resulted in dystocia. The evidence brought out so far, therefore, does not completely explain why the occipitoposterior position in contrast to the other vertex positions is associated with a higher incidence of difficulty in labor. To find the answer to this question we must turn to the details of the mechanism of the occipitoposterior position.

#### DESCENT, FLEXION, AND EXTENSION IN THE OCCIPITOPOSTERIOR POSITIONS

In Fig. 1 are contrasted the lateral views of an occipitoanterior and a true occipitoposterior position. These views include sufficient area to show the maternal pelvis and spine as well as the fetal spine and cranial ovoid. The x-rays were taken under similar conditions with the patient recumbent on her side between contractions. Two very characteristic differences stand out (Fig. 2). First, it is noted that a

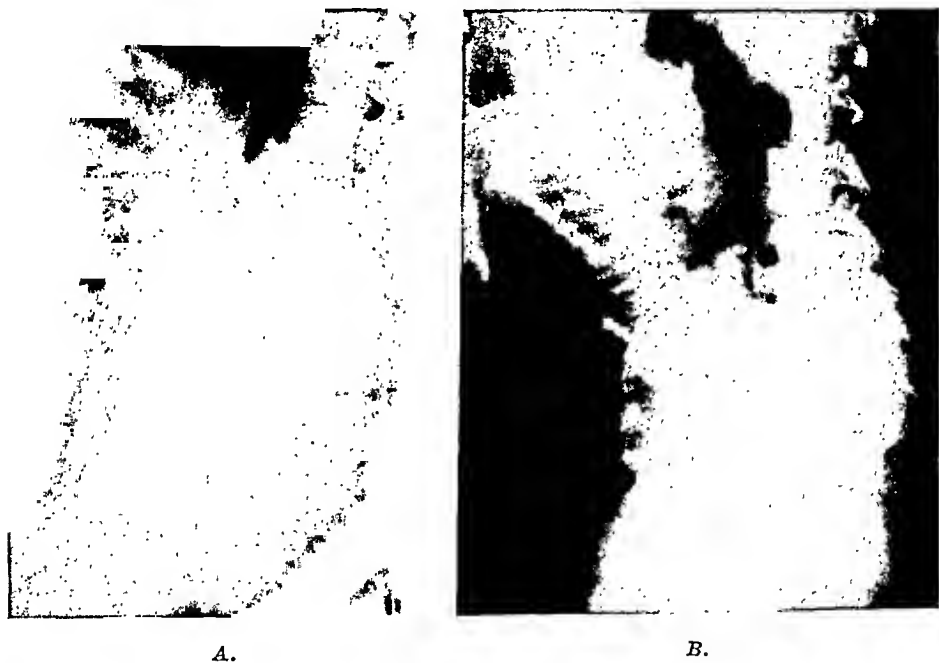


Fig. 1.—A, Lateral view, occipitoanterior position. B, Lateral view, occipitoposterior position.

line drawn through the fetal spine, while practically continuous as a straight line with the pelvic axis (AX) in the anterior case, is definitely at an angle with the pelvic axis in the posterior. Another difference is also obvious. In the anterior position, the cranial ovoid in a state of flexion presents its long axis more or less in the axis of the pelvis while in the posterior the length of the ovoid in extension runs more nearly across the pelvic axis. Repeated observations of similar lateral films have brought out the consistency of these fetal-maternal relationships in the true occipitoposterior positions.

While extension in the posterior position has been reported by practically every writer on the subject and seems to be a well-established aspect of the posterior mechanism, its cause has not been well understood. An explanation of this mechanism must begin with the assump-

the pelvis in which it occurs. In fact it could be argued that many occipitoposterior positions would meet with serious obstruction if they were forced to engage in any other position. For this reason there seems to be no justification for the prophylactic use of pads as advocated by Buist to correct an occipitoposterior position. Only when the posterior occurs in one of the well-formed round-inlet types in which an anterior position is theoretically just as favorable as the posterior does such a procedure seem at all justifiable. The physiologic normality of the occipitoposterior, however, does not remove the condition from the dystocia problem as the data obtained from our clinic show. We note that while 19 per cent of all vertex presentations engage in the posterior position, 44 per cent of the midforceps deliveries are associated with this position (Table I).

TABLE I. MIDFORCEPS IN RELATION TO POSITION OF ENGAGEMENT  
6440 Deliveries—283 Midforceps

INCIDENCE OF POSITION OF ENGAGEMENT IN 6440 CONSECUTIVE DELIVERIES		INCIDENCE OF POSITION OF ENGAGEMENT IN 283 MIDFORCEPS DELIVERIES	
O.T.	60.4%	O.T.	41.6%
O.P.	19.2%	O.P.	44.2%
O.A.	20.4%	O.A.	14.2%

Actually this concept of the etiology of the posterior position simply removes the emphasis from the position itself one stage back to the pelvis that caused it. This is shown clearly in Table II which is a comparison between the occipitoposterior positions that gave no particular difficulty and those that resulted in varying degrees of mid-pelvic arrests.

TABLE II. OCCIPITOPOSTERIOR POSITIONS. COMPARISON OF Pelves AND BABIES IN  
100 SPONTANEOUS AND 100 MIDFORCEPS DELIVERIES

	FETUS S LB.	MALE CHARACTER BRIM	BRIM UNDER AVERAGE	SACRUM FORWARD	CONVERG- ING SIDE WALLS	ARCH UNDER AVERAGE
Spontaneous	26%	23%	13%	15%	25%	23%
Midforceps	41%	31%	47%	34%	56%	36%

This leads us to conclude that large babies, small inlets, male characters, as well as the forward sacrum, convergence of the side walls, and narrow arches are distinct factors in the group which gave difficulty. The importance of the pelvis as a factor in the difficult labors associated with the occipitoposterior position has not received the attention which it deserves. Except for reports by Plass, Cosgrove, and Harper very little in the way of serious consideration has been given to this phase of the problem. A careful study of the pelvis in its entirety therefore will yield most valuable information upon which to base a prognosis of labor in these cases.

However interesting this comparison between the spontaneous and midforceps occipitoposterior deliveries may be, it should be borne in mind that a similar comparison in the other vertex positions would also bring out striking differences in the pelvis of the spontaneous



Since these anatomic points are fixed, it would seem impossible for extension ever to occur, for the lever arms cannot vary under these circumstances. This explanation of flexion, therefore, cannot be correct, since it does not permit an explanation of extension, which is an observed mechanism. In another and more reasonable explanation of flexion, the lengths of the lever arms are determined by projecting the line of force through the fetal spine and foramen magnum to the occipitofrontal plane. This is more nearly correct, since it permits of varying lengths of the lever arms depending upon the angle at which the force transmitted through the fetal spine is directed to the occipitofrontal plane. However, it is apparent that flexion and extension may take place even before the occipitofrontal plane becomes functional in the mechanism of descent. Actually it is upon the cranial plane of greatest friction that the forces which produce extension and flexion become operative and for this reason the mechanism is best explained by stating that flexion will result when the line of force through the fetal spine intersects the long axis of the cranial plane of greatest friction in such a manner that the frontal lever arm thus formed is longer than the occipital. Conversely, extension will result when the occipital lever arm is longer than the frontal. In Fig. 2 the cranial planes of greatest friction are planes *FR* and the line of force through the fetal spine meets this plane at *O*. It will be seen that the long arms are different in the two cases. In the anterior the long arm extends to the frontal region and is effective in producing further flexion, while in the posterior the long arm extends to the occipital region and results in extension.

From the foregoing it becomes obvious that the fetal axis along which the resultant expulsive force of the uterus is exerted is important first, because it may result in either an efficient straight line drive in the axis of the pelvis or one which is at an angle to the axis of descent with a partial loss of effective expulsive force, and second, because of the varying degrees of flexion or extension which it may bring about. To introduce a practical point, suppose the fetal axis in Fig. 2, *B* were to make a forward excursion as indicated. Now the lever arms become changed in their lengths and a flexion force is introduced. From these theoretical considerations, therefore, it should be desirable to maintain the fetal axis of the posterior position as far forward as possible. This can be helped by having the patient in labor maintain the upright position as long as it is possible for her to do so, since this favors a forward excursion of the back. While the upright position is the most favorable, it would seem that the supine position is the most disadvantageous for the occipitoposterior mechanism. When the patient finally must take to her bed, it would seem desirable that she should lie on her side in order to permit the forward excursion of the uterus during a contraction to be utilized to the fullest extent. It also seems obvious that binders are contraindicated. What is desired is the very opposite of what the binder achieves.

One of the factors responsible for the greater ease with which the multipara delivers the child in the occipitoposterior position may be the

tion that there is a downward force transmitted to the fetal head along the rigid fetal spine. This has been shown by Lahs, Olshausen, Warnkros, and others. They have stated that even when the membranes are not ruptured the effective force of uterine contraction and retraction is exerted largely by pressure of the fundus on the upper fetal pole and that this is transmitted directly to the presenting part by the vertebral column.

Some of the newer views concerning the behavior of the uterus during labor do not detract from the validity of this statement, for irrespective of the behavior of the uterine muscle there must be a resultant downward force which has the effect of changing the level of the fetus in the axis of the pelvis, and this force must be transmitted to the fetal

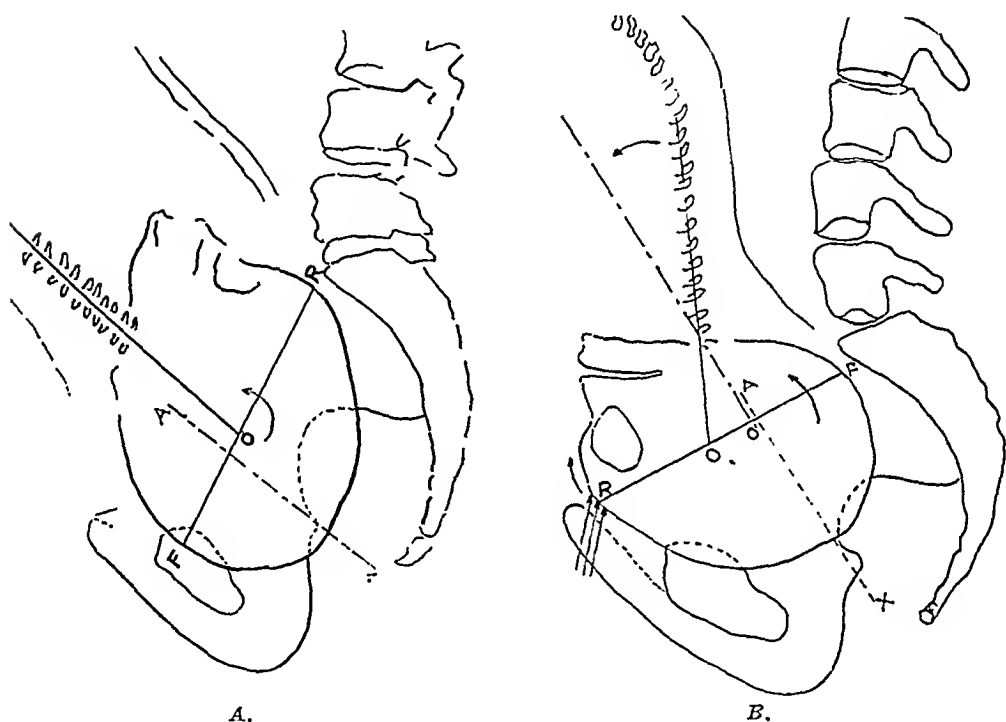


Fig. 2.—Direct tracing of Fig. 1.

head along the rigid fetal spine. This view is further supported by the frequent x-ray observation of the fact that with active labor the fetal spine becomes changed from a structure having a well-defined rounded curve to one which is straight and apparently rigid. This rigidity of the spine is maintained both during and between contractions. Now if this force is applied to the head at the foramen magnum it will result in both descent of the head and a torque motion around the atlas. This torque motion will produce either flexion or extension, depending upon the lengths of the two lever arms formed. A common explanation for the cause of flexion is that it results from the fact that the distance from the foramen magnum to the chin is longer than from the foramen magnum to the occipital protuberance, and that in accordance with the law of the lever the long arm will ascend when resistance is met by the head.

dilating and frequently fails to dilate completely even after a long labor. It would be beyond the scope of this paper to make any attempt to go into the causes of so-called cervical dystocia, but one fact becomes apparent when we study the lateral x-rays of the posterior positions and compare them with the anterior positions. If we consider the cranial ovoid as egg-shaped, it is noted that the point of the ovoid or its long axis is invariably pointed down when the position is anterior, while the long axis extends more nearly across the pelvis in the posterior positions. In Fig. 3 the cervix is located with lead-shot markers on each lip. The cervical canal must dilate and the lips retract over the head. The area over which this retraction has to take place is much greater in posterior positions of the head. This accounts for the frequently noted findings of a cervix, which although reasonably well dilated, seems to be far from the periphery of the head and remains as a definite and formidable rim all around. In addition to this it is possible that less efficiency in the dilating mechanism results from the fact that the cervix has to be retracted along a wide flat surface of the fetal head almost at right angles to the uterine axis in contrast to the more nearly vertical retraction over the long vertical oval of the well-flexed head.

#### FLEXION

From what has already been said, it becomes obvious that the lack of flexion is an important factor in the mechanism of the occipito-posterior position. The child's head eventually becomes flexed but this occurs only after a forward excursion of the fetal axis takes place. If we conceive of the previously discussed extension force acting unchecked, then, theoretically, the head should continue to extend until an equilibrium is reached when it cannot extend further. This would not occur until a full face presentation obtained. Long before this degree of extension takes place, however, the frontal region meets with resistance in the fore pelvis (arrows Fig. 2, *B*). Resistance at this point will completely check any further extension, since the fore pelvis acts as an unyielding block below the frontal bone. Let us assume further that the direction of force exerted through the fetal spine remains unchanged so that the lever action is still one of extension. It now becomes obvious that since further extension is blocked by the fore pelvis the only positive result of the uterine contractions is a backward and downward slide of the fetal head, resulting from the fraction of the force which is not dissipated in the blocked-up extension component. The counter force exerted by the fore pelvis against the frontal region of the head is not entirely passive, for we frequently note that it results in a good deal of molding by pushing the frontal bones under the parietals at the very point where the pressure is exerted (see Fig. 13). This same force acting over a long period of time may eventually pinch off the stretched cervix, resulting in passive congestion and edema of the anterior lip.

Depending upon the amount of available space in the upper pelvis, the head moves down in the extended position, sometimes quickly,

forward excursion of the uterus and the fetal back resulting from the greater relaxation of the abdominal walls. This should favor flexion and a better axis of drive. This same forward excursion of the fetus may take place when the membranes rupture. The marked improvement in the efficiency of labor which followed the rupture of the membranes in several of our cases may have been due to this cause. Theoretically then, rupture of the membranes may favorably alter the pattern of labor by causing the fetal back to go forward. It will be of interest to study this in detail later on.

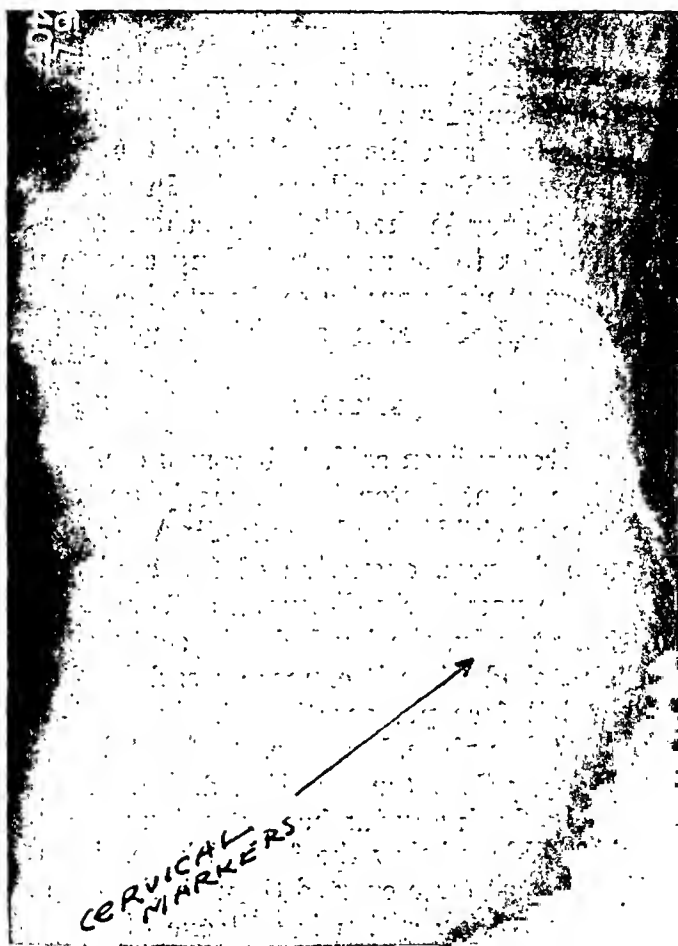


Fig. 3.—Lead shot markers sutured to anterior and posterior cervical lips, R.O.P. position. Cervix 2 cm. dilated.

A point about extension which is clinically important is the fact that when the head is in extension the frontal region frequently bulges above the symphysis and gives the impression of disproportion. It has been found repeatedly that in many such cases when the patient assumes the upright position for the lateral x-ray film, the level of the head changes remarkably and frequently appears well engaged. Much profitable information can be obtained by suprapubic palpation in the upright position when the head is unengaged.

One of the difficult problems in the occipitoposterior position is the behavior of the cervix. It is well known that the cervix is slow in

## ROTATION

When the matter of internal rotation as related to the occipitoposterior positions was considered, it seemed necessary to reinvestigate its causes, since it seemed obvious that the present concepts of this important mechanism did not account for the observed facts. It soon became apparent that this was the real nucleus of the investigation for the reason that practically all the arrests occurred with the head unrotated and that therefore a good deal of the dystocia could be related to a failure of this mechanism. Also from a practical point of view it



Fig. 4.—Head in R.O.A. position at onset of labor became adjusted to R.O.P. position as labor advanced.

seemed obvious that a complete understanding of the details of rotation would be important, since we are frequently called upon to re-duplicate this mechanism in the course of an operative delivery, and unless we fully understand its underlying cause and the reasons for its failure, we are not equipped to carry out many of the more difficult obstetric operations.

The theory of internal rotation which at the present time is most generally accepted was first considered by West in 1856. He stated that the head was rotated by the inclined planes of the pelvic floor and that whatever part of the child reached the pelvic floor first was rotated to the front. On the basis of this theory the head will always turn to the front except in those posterior positions with deflexion, in which case the sinciput will rotate to the front while the occiput rotates posteriorly. There has been little objection to this concept of rotation,

more often slowly, and occasionally not at all under the impulse of only a fraction of the uterine force. Now as the head slowly descends downward and backward, the fetal back, being limited by the posterior uterine wall, must accommodate itself to the lower position of the fetal head by moving forward. This changes the lengths of the lever arms as previously illustrated and a flexion force is introduced. While this forward excursion of the fetal back may take place solely from the increased rise of the uterus as the contractions become stronger, it usually does not occur until a sufficient amount of descent has taken place to force the fetal back forward. As a consequence it is noted that complete flexion does not usually take place until the head is well down in the pelvis. This mechanism of flexion goes on slowly as the fetal axis moves forward in response to the descent of the head. Flexion, therefore, is ultimately dependent upon descent of the fetal head. When the upper pelvis is abnormal in either shape or size, it interferes with descent and this in turn prevents proper flexion thereby multiplying the difficulties. When the pelvis is ample, even the partially extended head will descend without much difficulty, become flexed, and there is a comparatively easy labor. An abnormal pelvis and a posterior position may therefore react upon each other to produce a really difficult labor.

As will be shown later, many of the so-called midpelvic arrests occur because of factors existing at the brim. When preparing to do a mid-forceps operation with the head in the posterior position and definitely extended, the conditions prevailing at the brim should always be considered, even though the lowest part of the molded head seems to be fairly well down in midpelvis.

Since flexion is so important, we naturally want to know how it may be brought about. Posture of the patient has already been considered. Pressure against the frontal bone carried out with each pain under nitrous oxide anesthesia should be helpful if the procedure is carried out over a sufficiently long time. Manual stretching of the cervix may be combined with this when dilatation has come to a standstill. In this way, by removing the resistance of the soft tissues, the full effect of that fraction of the uterine force which is not dissipated in extension is applied to bringing the head lower in the pelvis, which in turn will bring the back forward. Since this will result in greater flexion and smaller presenting diameters, it will be followed by more descent and so a favorable chain of events may be initiated.

Flexion will also follow a change of the fetal axis by turning the child completely, both head and shoulders, to an anterior position following which the patient is allowed to have further labor. Douglas Miller has advocated this method, and although we have no experience with it, there is reason to endorse its mechanical soundness. However, it should be stated that such a procedure would be feasible only when labor has progressed sufficiently to allow molding of the fetal head, otherwise the unmolded head would meet the very resistance in the fore pelvis which caused the posterior position to occur in the first place.

In Fig. 5 we note an example of internal rotation. The fetus descended in the transverse position R.O.T. to the level of the spines, and because the prominent spines offered resistance in front while the sacrum was directed well backward, we find the occiput moving into the roomy posterior segment to become a secondary right occipitoposterior position. The head in this case did not rotate to a posterior position according to West's theory, because it was extended since it was partially flexed. It apparently rotated posteriorly, because there was more room for the occiput in that part of the midpelvis than there was anteriorly. Internal rotation, therefore, is influenced to a large extent by the shape of the pelvis.

To state the facts about internal rotation briefly it may be said that under the influence of the inclined planes of the pelvic gutter which initiate the mechanism, the vertex will tend to turn anteriorly when the head reaches the pelvic floor in an oblique anterior position and conversely will tend to turn directly posteriorly when the head reaches the pelvic floor in an oblique posterior position, if the pelvis permits. The inclined planes of the pelvic floor therefore while responsible for rotation do not determine in what direction rotation will occur. According to this concept of internal rotation when the head reaches the pelvic floor in an obliquely posterior position, it will always tend to rotate directly posterior. In the average case, however, such rotation is resisted by the sacrum and the strong sacrospinous ligaments and occurs only when the lower sacrum is well backward and has an ample concavity as well. This was an observed fact in practically all the cases of direct occipitoposterior rotation in this series. Under these circumstances even a fairly large head may rotate posteriorly and in the presence of an average sacral inclination, a small child may also rotate in this way. This explains why so many small babies become direct occipitoposteriors.

In addition to these sacral characteristics, posterior rotation to the hollow of the sacrum requires that the upper pelvis have a sufficiently long A.P. diameter to accommodate the brow which is considerably in advance of the occiput when the head is extended.

We next inquire into what happens when, by virtue of the resistance offered by the sacrum and the sacral ligaments and muscles, the obliquely posterior vertex cannot follow its natural inclination to rotate further in that direction to become a direct occipitoposterior. Suppose we first assume that the head will simply attempt to descend further in the oblique O.P. without rotational change of direction. Now it can be easily demonstrated that if a fetal head is placed in the pelvis as an oblique posterior in a partially deflexed attitude as they invariably occur and an attempt is made to push the head downward in this position, say an R.O.P., it will be found that the face or the brow of the child comes in contact with the left fore pelvic brim which prevents it from proceeding further in this direction (Fig. 6). So we may conclude that under the conditions previously mentioned the head moves downward in an oblique O.P. until the brow meets with resistance at the brim at which point the brow slides backward along the pelvic brim, again following the path of least resist-

because it seems to explain satisfactorily for the first time the mechanism of short rotation to the hollow of the sacrum. In the light of our present investigation, however, there are some objections to this theory, for it seems that many posterior and transverse presentations that are not extended rotate backwards. In other words, the direction of rotation does not depend directly upon flexion or extension.

In fact a searching study of all the theories on the cause of internal rotation leaves one with the thought that there is no single theory that explains all the phases of this mechanism satisfactorily. With this in mind an attempt was made to see if the material in this study could provide a more complete explanation of this important mechanism. Before presenting these views on the subject, it might be well to call attention to a simple form of rotation which has been frequently noted to occur at the brim before engagement (Fig. 4). The case shown in Fig. 4 started labor with the head dipping into the brim in the R.O.A.

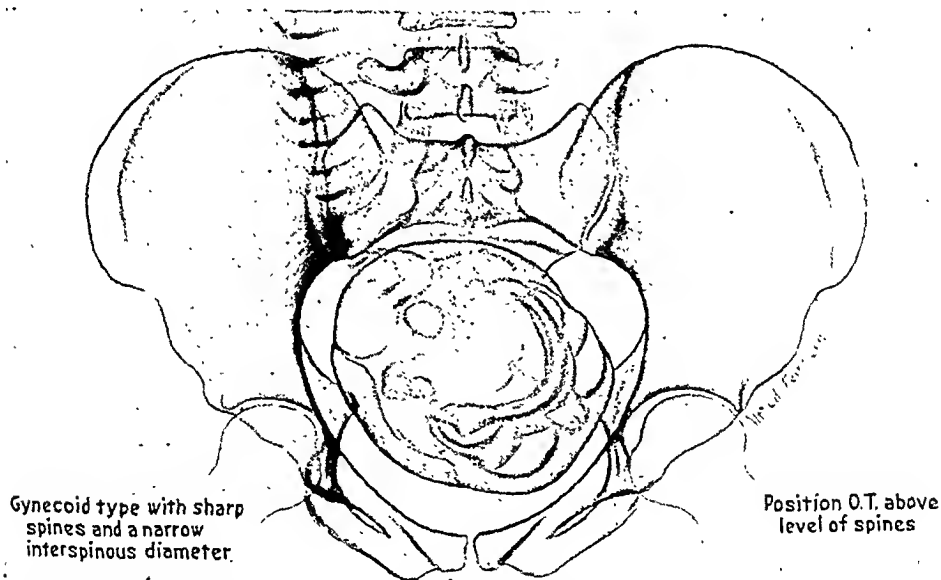


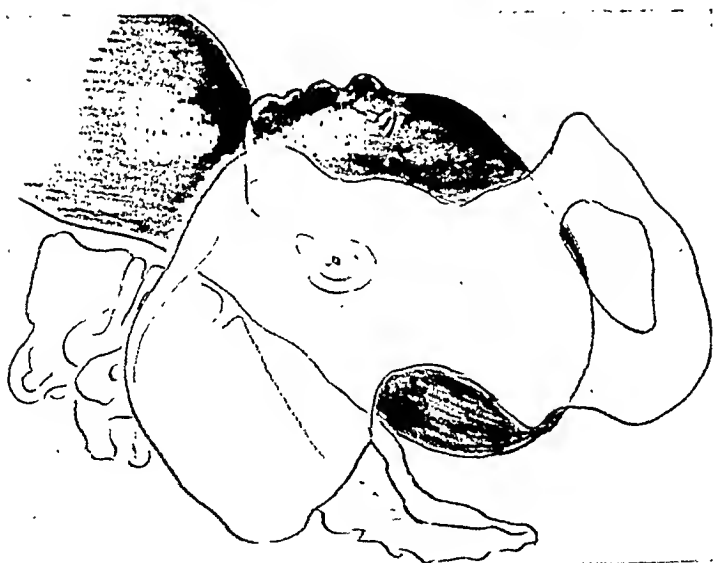
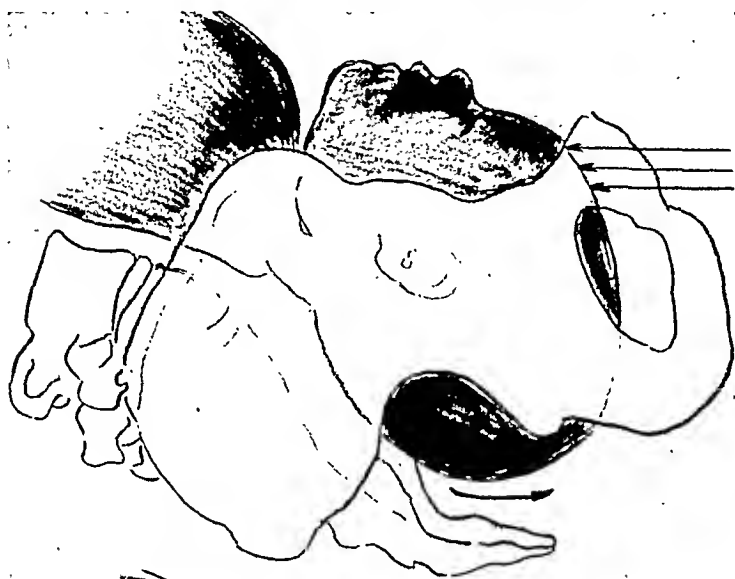
Fig. 5.—Secondary oblique occipitoposterior position. Occiput rotated from an R.O.T. to an R.O.P. position moving away from the resistance of the spines in front into ample posterior sagittal diameters at the interspinous level.

position, but under the influence of labor the head adjusted itself to the optimum diameters and finally engaged in the R.O.P. position as illustrated. It may be said that the rounded surfaces of the fetal head sliding easily against the curvatures of the inlet results in adjustment of the head in a position which offers the least resistance to its engagement.

Although this is not an example of internal rotation, it serves to illustrate a form of simple rotation at the brim, better referred to as adjustment. It simply means that the head, meeting obstruction, is forced along the path of least resistance. Now, to some extent, we are dealing with the same conditions at the interspinous level where internal rotation most often takes place, although the factors which resist and those which favor rotation are more involved.



To return to those posterior arrests that are caused by a narrow brim preventing rotation (Fig. 7), the detailed study of the mechanism in those cases shows that they may correct themselves by a mechanism of flexion. If the forces of descent continue, then flexion occurs, because while the resistance of the face or brow against the upper fore pelvis



B.

Fig. 8.—Failure of rotation caused by narrow pelvic brim as in Fig. 7 may correct itself by a mechanism of flexion. Forepelvic obstruction (arrows) is relieved by flexion and head is allowed to rotate.

holds the upper part of the vertex fixed, the occiput is being forced downward away from the sacrum. This forward excursion of the occiput results not only in flexion but also eventually in a recession of the brow from the narrow fore pelvis. As a result of these changes, further

ance in a manner similar to the mechanism of "adjustment" previously discussed. This, of course, makes the occiput turn forward to a transverse position. From this transverse position, the occiput will then move forward and downward on the inclined planes of the pelvic floor to the anterior position provided again that the shape of the pelvis permits. If the brim is transversely narrowed, as in an anthropoid pelvis, it may be impossible for the brow to move backward and a posterior arrest is the result (Fig. 7). It must be noted, however, that while conditions may be favorable for backward rotation of the brow at the brim there

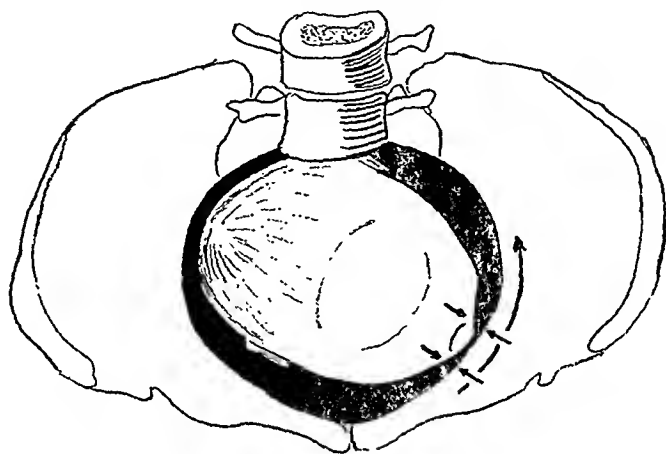


Fig. 6.—If the partially extended oblique posterior were to continue its descent without change of direction, the facial aspect of the head would meet obstruction in the fore pelvis as indicated by the arrows.

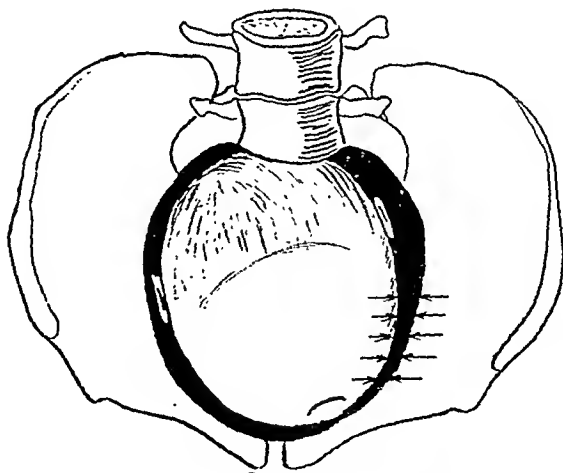


Fig. 7.—A narrow pelvic brim may be the cause of failure of rotation in a posterior position and cause it to become arrested.

may be obstruction to forward rotation of the occiput by prominent spines or convergence of the lateral walls of the pelvis (Fig. 9). It may be said, therefore, that rotation toward the front in a posterior position will occur when the head is forced away from the limiting posterior boundaries of the sacrum providing that the relations of the brow or face to the brim and those of the occiput to the spines and side walls of the pelvis permit.

If labor must be terminated it becomes most important to recognize the relationship between the long oval of the head and the long oval of the inlet and realize that rotation cannot be accomplished at the level of arrest. Displacement of the head upward as in a version or as recommended by Pomeroy becomes the method of choice in those cases.

Another form of arrest is that which results from the fact that the occiput cannot rotate forward because of prominent spines. These cases arrest in the R.O.P. position and must be handled according to the type of pelvis in which the prominent spines are found. When the narrow

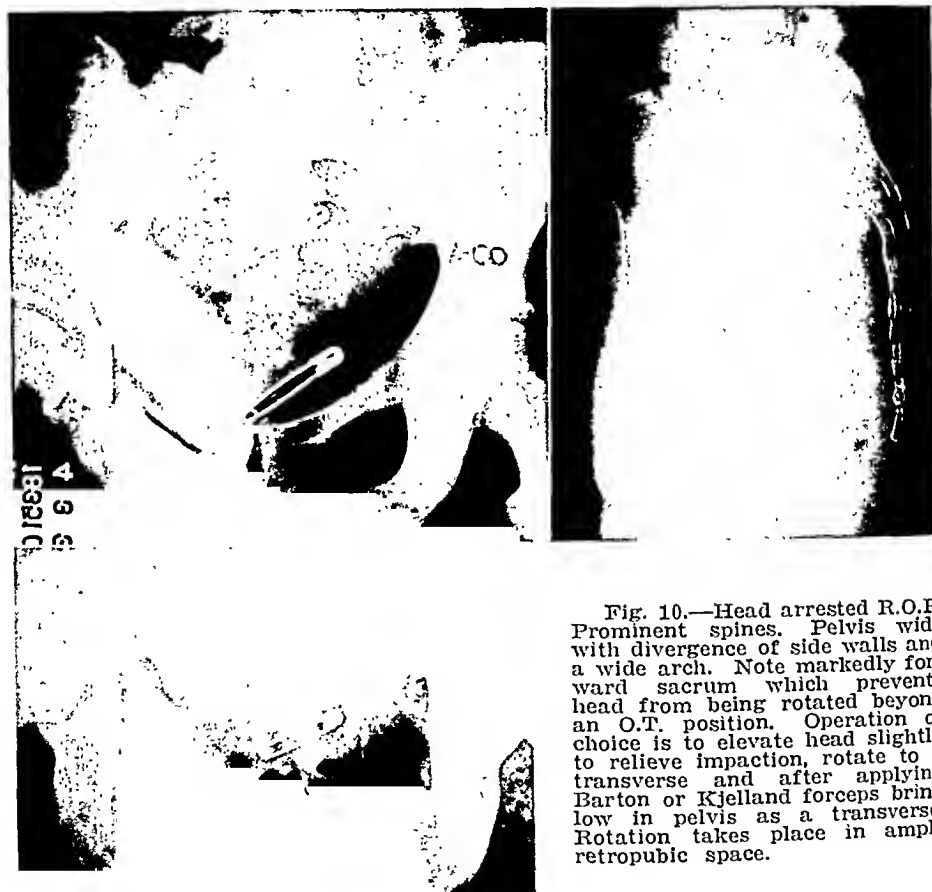


Fig. 10.—Head arrested R.O.P. Prominent spines. Pelvis wide with divergence of side walls and a wide arch. Note markedly forward sacrum which prevents head from being rotated beyond an O.T. position. Operation of choice is to elevate head slightly to relieve impaction, rotate to a transverse and after applying Barton or Kjelland forceps bring low in pelvis as a transverse. Rotation takes place in ample retropubic space.

spines are associated with a general narrowing of the entire pelvis (Fig. 9), the head must be pushed up, free of the brim, and rotated and brought down in an anterior position. On the other hand, when the prominent spines are associated with a pelvis that has a flat posterior segment (Fig. 10), the head can be manually rotated to an O.T. position after lifting it slightly above the level of impaction against the spines and since the flat posterior segment will not allow it to go any further than an O.T., Barton or Kjelland forceps are applied to the head in this position. Then, by lateral flexion, the head is brought into the retropubic space away from the spines where low rotation can be accomplished. This technique, however, requires good transverse width in

progress may be expected because the impaction of the brow on the upper pelvis is relieved and this allows the brow to rotate backward slightly while concomitantly the occiput moves forward and downward. By virtue of this seesaw action of the head (Fig. 8), the upper brow moving away from the fore pelvis and consequently being enabled to slide backward, rotation may eventually take place if the brim is not excessively narrow.

Flexion is of added advantage and further aids this mechanism because it changes the cranial girdle of contact from the occipitofrontal plane to the suboccipitobregmatic plane so that the cross section of the fetal head within the brim is changed from a long oval to a circle.

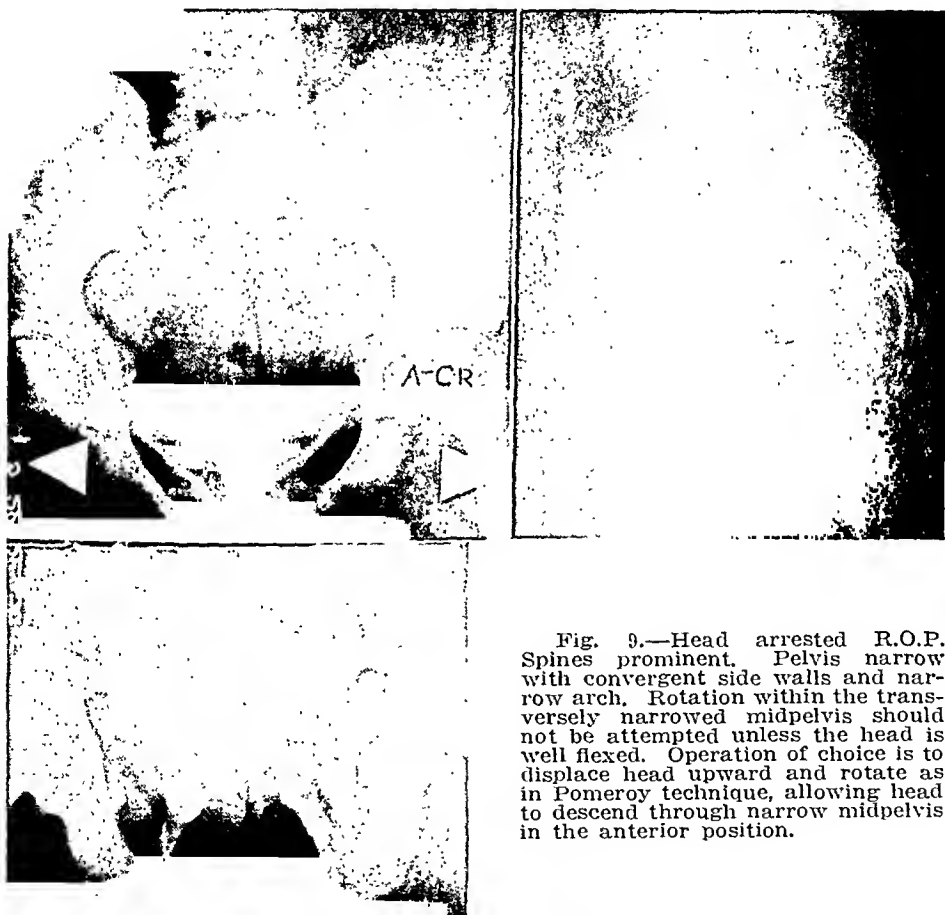


Fig. 9.—Head arrested R.O.P. Spines prominent. Pelvis narrow with convergent side walls and narrow arch. Rotation within the transversely narrowed midpelvis should not be attempted unless the head is well flexed. Operation of choice is to displace head upward and rotate as in Pomeroy technique, allowing head to descend through narrow midpelvis in the anterior position.

This type of arrest then is due primarily to the fact that the brim, being transversely narrowed, does not easily permit that part of the head which is still within it to turn. Since a cross section of the plane of the vertex that is within the brim is a long oval and coincides with the shape of the brim and since it is impossible to turn one long oval within another oval which it closely fits, a change of conditions must be set up if delivery is to be accomplished. We have just seen that this may occur spontaneously by a mechanism of flexion and this might be the first maneuver that suggests itself. Unfortunately manual attempts to bring this about often fail because we cannot always do with the hand what nature accomplishes only after hours of tedious labor if at all.

saeral resistance and traction in the posterior position may result in injury to both mother and child (see legend Fig. 11).

A word should be said about those cases that rotate directly posterior (Fig. 12). While it has been previously stated that they represent evidence of ampleness of the saeral concavity and of the posterior sagittal diameter at the level of the spines, the saeral tip may come forward and so cause a direct O.P. arrest low in the pelvis. This type of arrest is usually handled quite easily by manual rotation to an O.A., for the head is low and flexed so that rotation is usually easy. Whether the sacrum encephalizes or not, it does not seem justifiable to deliver direct O.P. arrests face-to-pubis, except in the very occasional case in which there is more room in the posterior sagittal diameter than the average.

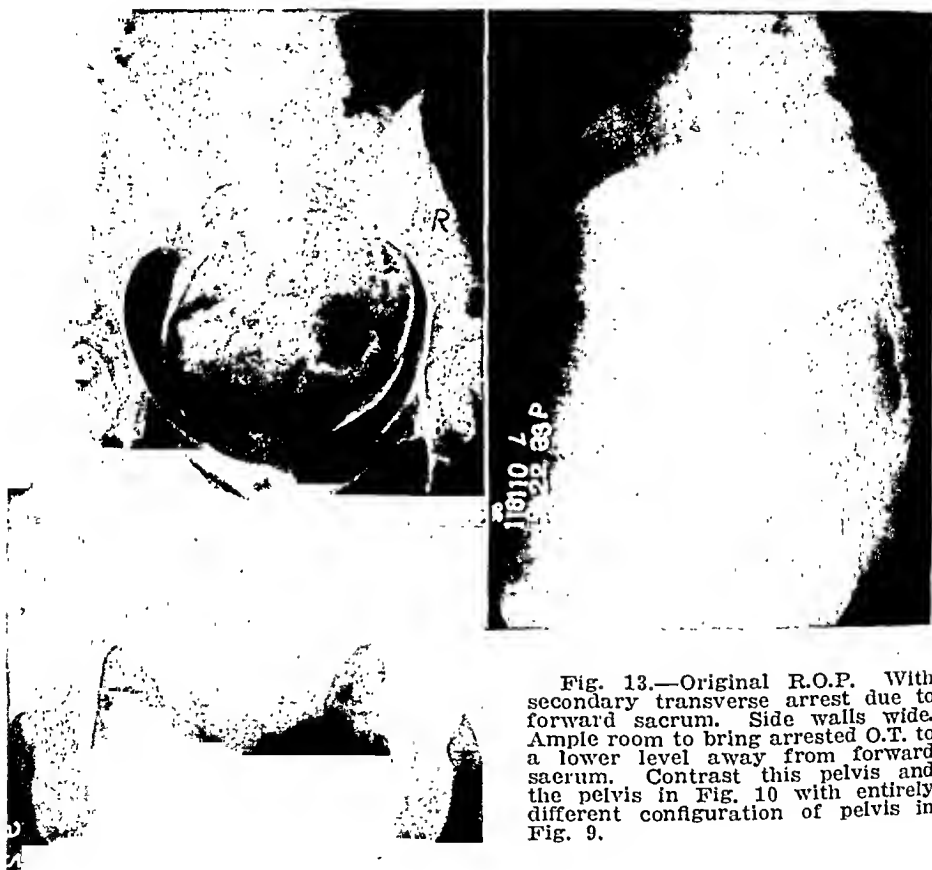


Fig. 13.—Original R.O.P. With secondary transverse arrest due to forward sacrum. Side walls wide. Ample room to bring arrested O.T. to a lower level away from forward sacrum. Contrast this pelvis and the pelvis in Fig. 10 with entirely different configuration of pelvis in Fig. 9.

After rotating to an O.T. the head may fail to rotate further. The failure of the head to rotate further than a transverse may be due to: (1) An inlet with flattening in the posterior segment; (2) a forward sacrum. Secondary transverse arrests of the first variety most frequently occur in android or android-anthropoid pelvises. The head engages in the occipitoposterior position and when rotation to the hollow of the sacrum is prevented by the resistance of the sacrum behind, the occiput rotates forward but frequently becomes arrested part way and remains as an occipitotransverse; the flattening of the pelvic brim has prevented it from turning further. The flat posterior segment of the

front of the spines to allow the head to be brought down into the retro-pubic space as a transverse.

These oblique occipitoposterior arrests in contrast to direct occipitoposterior arrests may be seriously mishandled by attempting to pull the head down in the posterior position. The fact that the head remains obliquely O.P. and does not rotate directly posterior is evidence of



Fig. 11.—Case illustrates why oblique posterior arrests should not be brought down in the posterior. Manual rotation and Scanzoni failed due to transverse narrowing, then brought down O.P. with injury of sacral plexus and abrasion of child's forehead. An oblique posterior arrest in itself is evidence of restricted space posteriorly. Displacement upward and rotation above brim should have been procedure of choice.

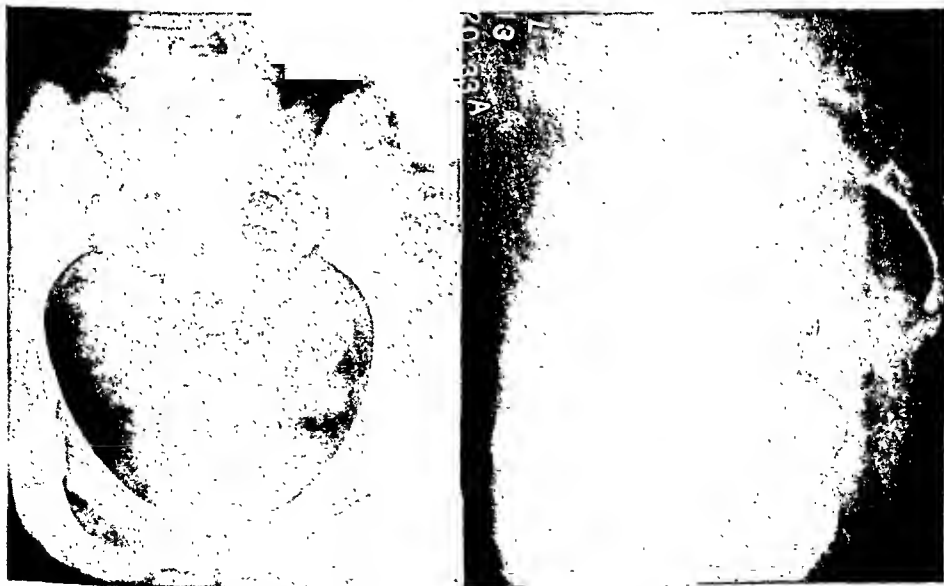


Fig. 12.—Direct occipitoposterior arrest. Direct occipitoposteriors give evidence of sacral amplexness at the level of the spines but not necessarily below that. Forward sacral tip does not permit traction of head in direct posterior. Manual rotation usually easy because head is low and usually well flexed.

3. Occipitoposterior positions, although physiologic and in spite of the fact that 70 per cent deliver spontaneously, cause more dystocia than the other vertex positions.

4. Dystocia in posterior positions originates with the abnormality of the pelvis in which they occur.

5. Extension is a common feature of the posterior mechanism and is caused by the posterior axis of fetal drive. Extension not only results in larger presenting diameters but also causes a part of the uterine drive to be dissipated.

6. Flexion greatly facilitates the mechanism and should be encouraged by posture. A forward excursion of the fetal axis must take place before flexion can occur.

7. Internal rotation although receiving its impulse from the inclined planes of the pelvic floor receives its directional force from the variable resistances offered by the bony pelvis in all the pelvic planes through which the head is descending.

8. Since the pelvic architecture shows marked variations in shape, it follows that the patterns of rotation show corresponding variations.

9. Emphasis is placed on the importance of recognizing two fundamentally different pelvic forms frequently associated with posterior positions, viz., those forms in which the transverse diameters are contracted at the brim or midpelvis or at both levels with compensating amplexity in the anteroposterior diameters and the converse of this form in which the anteroposterior diameters are shortened by virtue of a flat posterior segment at the brim or a forward sacrum at the midpelvis level while the transverse diameters remain ample. It follows that operative techniques should be individualized for each type.

10. The occipitoposterior mechanisms which have been reviewed may be translated into operative principles as follows:

a. When the posterior arrest is due to a narrow anthropoid pelvic brim preventing rotation, the head is pushed up and rotated above the brim. Version is also correct in principle.

b. When arrest is due to narrow spines in definite anthropoid types, the head is pushed up and rotated above the spines or above the brim. Version is also an alternative procedure.

c. When the posterior aspect of the inlet is flat or the sacrum is forward, rotation is carried to the transverse only and in this position the head is brought into the lower fore pelvis or the retropubic space thereby converting it into a deep transverse. Rotation is carried out at this low level. Upward displacement of head with rotation and version are incorrect procedures.

d. When the posterior aspect of the inlet is flat or the sacrum is forward and labor has progressed sufficiently to allow a deep transverse arrest to occur rotation is again carried out at a low level just behind the pubis.

e. When the head is arrested in a direct occipitoposterior, deliver without rotation only when the lower sacrum is not encroaching. In most cases the head should be rotated to the anterior. Such rotation is carried out at the level which is most suitable for the pelvis in which it occurs.

inlet in these cases exerts an effect which is comparable to the transversely contracted inlet in the oblique posterior arrests. Rotation can take place only after the head has descended lower in the transverse so that the obstruction caused by the posterior flattening of the pelvis is cleared. In Fig. 13 the original presentation was R.O.P. It became arrested in the R.O.T. position and while it should have been brought down lower in this position, it was unfortunately pushed up, rotated to a direct anterior, and delivered as such with a great deal of difficulty. The child survived although it was a shocking type of delivery. Here we note that the Pomeroy principle of rotation, so ideally suited in the transversely narrowed pelvis, becomes undesirable because the contours of the pelvis demand an entirely different mechanism.

It is obvious, therefore, that these transverse arrests of an original posterior position, referred to as deep transverse arrests when they occur low in the pelvis, may be explained by the architecture of the pelvis. Actually these cases give evidence that a correct mechanism is being naturally followed, the low transverse position being maintained by the flat posterior segment of the inlet or a forward sacrum in the presence of ample transverse diameters. Nature seems to point the way. Traction in the transverse with lateral flexion into the lower retropubic space where rotation is brought about is the usual method of choice. These cases are more difficult to interpret when arrest takes place at a higher level in the pelvis when the vertex is still in the obliquely posterior position. The transverse mechanism that should obtain in the lower pelvis has not been indicated by the position of the head and can be determined only after a complete appraisal of the entire pelvic architecture.

The various mechanical principles that have been applied to the operative treatment of the difficult types of arrests under discussion are of considerably more importance when the head is extended and unmolded than when the head is flexed and well molded. In the well-flexed head all the cross sections throughout the entire head at right angles to the axis of descent become spheroids which meet with equal resistance no matter how the head is turned. But in the majority of posteriors that become arrested, such flexion is not complete and for this reason the presenting anteroposterior diameters of the fetal head are longer than the transverse diameters. Since it has been shown that the pelvic types in which posteriors may occur vary markedly in the ratio between their available anteroposterior and transverse diameters at all pelvic levels, it naturally follows that each posterior arrest requires correct adaptation of the longer cephalic diameters to the correspondingly longer pelvic diameters.

#### SUMMARY

1. The occipitoposterior position in the main is caused by the adaptation of the head to a pelvis having a narrow fore pelvis and an ample anteroposterior diameter and therefore may be considered "physiologic."
2. Degrees of the posterior position can be differentiated. A true posterior position is one in which the occiput is at or posterior to the sacroiliac synchondrosis.



and transverse relationships remain not greatly changed, the general appearance resembling the conformation of that seen in childhood. Thus, we find variations in the adult pelvis, and in general these variations are: (a) those whose essential anteroposterior diameters are relatively longer than the transverse diameters, (b) intermediary states, and (c) those whose essential transverse diameters are relatively longer than the anteroposterior (Figs. 1 to 4).

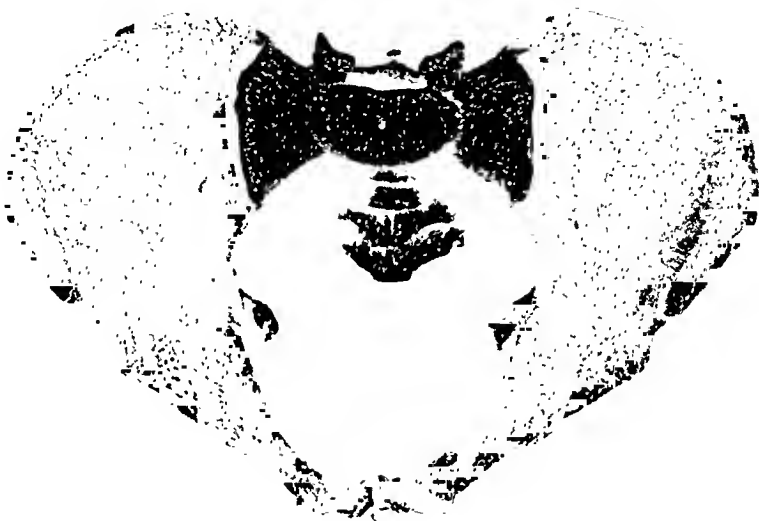


Fig. 1.—Dolichopellic type: anteroposterior of inlet, 12.5 cm.; transverse of inlet, 11.8 cm. (Male pelvis.)



Fig. 2.—Mesatipellic type: anteroposterior of inlet, 11.3 cm.; transverse of inlet, 12.3 cm.

These changes in anteroposterior and transverse relationships probably result from the influence of various factors: hormonal, hereditary, environmental, and mechanical. Just what part the first two play may be only conjectured, but the force of environment in influencing pelvic

f. When the head is low, well-molded, and well-flexed manual rotation is the most desirable procedure.

g. Rotation at level of arrest is rarely a procedure of choice because in most instances there is some pelvic obstruction which is preventing rotation at that level.

h. The unmodified Scanzoni maneuver with simultaneous traction and rotation initiates the act of rotation at the level of arrest where there is obstruction. It is, therefore, an undesirable procedure in those cases which have a well-molded and flexed head. Even in this group of cases manual rotation is the operation of choice.

I wish to acknowledge my deep appreciation for the many helpful suggestions offered by Dr. W. E. Caldwell in the course of this study.

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## THE CLINICAL APPLICATION OF ROENTGEN PELVIMETRY AND A STUDY OF THE RESULTS IN 1,100 WHITE WOMEN\*

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WITHIN the past decade the application of roentgen techniques to the study of the female bony pelvis has resulted in a definite revision of our views concerning the conformation of this structure and its relation to the process of childbirth. As a result of roentgen studies in adolescents and adults, we now possess certain knowledge of pelvic variations and this information permits their adequate description and ready identification. A comprehension of this newer knowledge is of importance to the obstetrician, for he will find advantages in applying it to many of his clinical problems.

It is the purpose of this paper to endeavor to clarify the subject, to review its more important aspects and to survey certain data obtained from the study of a comparatively large group of primiparous patients in whom a roentgen survey of the pelvis has been made.

### THE PELVIS AS A WHOLE

It is important in considering the pelvis as a whole to consider some of the fundamentals of pelvic architecture. The pelvis of the newborn shows essential differences from that of the adult. In the former the pelvis is relatively longer anteroposteriorly and relatively shorter transversely. This applies to the entire bony pelvic canal throughout its course from inlet to outlet. During growth through childhood and particularly during adolescence, certain changes in these anteroposterior and transverse relationships usually take place. In some individuals such changes are relatively extensive, the anteroposterior relationships becoming definitely shortened while the transverse relationships become relatively longer. In other individuals such changes are less extensive, and in many individuals these anteroposterior

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flattened forms of pelvic inlet may arise as a result of either of two mechanisms; an excessive growth laterally that is of the transverse diameter or a diminished growth anteroposteriorly. A comparison of the mean dimensions of the inlet from the various types in our series sheds some light on this question.

MEAN VALUE FOR DOLICHOPELLIC		MEAN DIFFERENCE AS COMPARED WITH DOLICHOPELLIC		
		MESATYPELLIC	BRACHYPELLIC	PLATYPELLIC
Anteroposterior	12.59 cm.	-0.73	-1.52	-3.24
Transverse	11.92 cm.	+0.46	+0.89	+0.86

Thus, it seems apparent that the lessening or incomplete development of the anteroposterior diameter is the more important mechanism, and increasingly so as the degree of flattening becomes more extreme.

For purposes of the classification of pelves to be discussed later, we may say that the tendency of a pelvis to retain most of the relationships of fetal and childhood conformation and thus remain relatively "elongated" anteroposteriorly may be spoken of as dolichopellism (dolicho-long), while the tendency in a pelvis to become relatively broader transversely and short anteroposteriorly is that toward platypellism (platy—broad or flat).

#### MALE AND FEMALE PELVES

Although, as we have shown,<sup>2</sup> the same general variations occur in the adult pelves of both sexes, there do occur in both certain differences which are designated as sex characteristics. An understanding of the essential sexual differences between male and female pelves may be tabulated as follows:

MALE	FEMALE
Heavier, rougher, more massive bones	Greater size, lighter build
Lessened capacity of pelvic inlet	Greater capacity of pelvic inlet
Narrower pubic arch, more angular	Greater width of pubic arch
Sidewalls converge	Larger interischial width
Smaller notch. Boundaries meet above in acute angle	Great sacrospinous notch, large, almost rectangular
Sacrum placed more anteriorly toward pelvic axis	Sacrum placed more posterior to pelvic axis
Pelvic height greater	Pelvic height less

It has been shown that certain characters resembling those seen in male pelves may occur in female pelves, and when this happens such changes may have definite obstetric significance. These characters in general may be stated:

1. Long narrow sacrospinous notch with sacrum in a more forward position lessening the space in the posterior pelvis.
2. Narrow subpubic angle and lessened transverse diameter of outlet.
3. Convergency of pelvic sidewalls from above downward restricting room in mid and lower pelvis.
4. A tendency toward angulation in the inlet at or near the sacro-iliac junction with a somewhat posterior displacement of the transverse diameter.

architecture is definitely seen in the well-known changes due to rachitic influence. The influence of an environmental factor is also strongly suggested in our comparative studies in women of the college group and those of the clinic group.<sup>1</sup> The mechanical factors are those related to posture, muscular action, etc.



Fig. 3.—Brachypellic type: anteroposterior of inlet, 9.8 cm.; transverse of inlet, 12.4 cm.



Fig. 4.—Platypellic type: anteroposterior of inlet, 10.0 cm.; transverse of inlet, 14.7 cm.

As stated above, the shape of the pelvic inlet in early childhood is characteristically elongated anteroposteriorly, or dolichopellic, and if a pelvis of this type were to grow symmetrically, it would obviously have a similar shape in adult life. From this it would appear that the round or

## THE MIDPELVIC PLANE

This plane, somewhat ovoid in form, is large anteriorly and somewhat restricted posteriorly, being narrowed by the convergence of the sacrospinous ligaments. It is bounded anteriorly by the lower border of the symphysis, laterally by the ischial spines, and posteriorly by the lower third of the sacrum, usually at the junction of the fourth and fifth sacral segments. Three diameters are of obstetric significance:

1. The anteroposterior diameter
2. The transverse or bispinous diameter
3. The posterior sagittal diameter

*The anteroposterior diameter:* From a point on the lower border of the symphysis this diameter extends posteriorly at the level of the ischial spines, usually falling to a point at or near the junction of the fourth and fifth sacral vertebrae.

*The transverse diameter* is the narrowest distance separating the ischial spines.

*The posterior sagittal diameter* is that part of the anteroposterior diameter which lies posterior to its intersection by the transverse diameter.

## THE PELVIC OUTLET

It must be remembered that the pelvic outlet consists essentially of two planes represented by two triangles, the bases of which join each other at the lowermost points of the tubera ischia. For many years a bituberal diameter has been described and used as an index to outlet capacity, and extending posteriorly from a midpoint on this diameter a posterior sagittal diameter of the outlet has also been described. At the present time I am convinced that the mensuration of the so-called bituberal diameter is so variable that definite measurement by either palpatory or roentgen methods is very questionable. This is because of a lack of definite end points. It is, indeed, true that contractions of the outlet and narrowing of the tubera ischia may and should be recognized clinically by palpation, but the mensuration of such contraction in terms of a bituberal diameter is difficult of proper determination. For this reason I recommend the employment of the so-called widest diameter of the outlet as described by Caldwell, Moloy and D'Esopo.<sup>3</sup> It is possible to determine this measurement with considerable exactness by roentgen methods and, taken in conjunction with the palpatory evaluation referred to, it should serve as a good index to pelvic capacity in this portion of the pelvis (see Dimension E, Fig. 5).

Another dimension which has interested us recently is that known as pelvic height or depth. Schuman,<sup>4</sup> in 1934, pointed out the value of this dimension, stating that clinically the most important characteristic of the male, funnel or high assimilation pelvis is its increased depth. This dimension is the perpendicular distance from the tuberosity of the ischium to the iliopectinal line. Schuman designated this as "the pubotuberous diameter" (see Dimension E, Fig. 6). This author quotes Todd's results in 53 white male and 50 white female pelvis with averages of 101 mm. and 90 mm., respectively. In a series measured roentgeno-

Narrowing of the forepart of the pelvic inlet has been described by some authors as a definite male characteristic, and I agree that this is seen in many male pelves, but it is by no means constant, for the majority of the pelves in our study of adult males showed a forepart as wide relatively as that seen in female pelves. Again it should be emphasized that in neither male nor female pelves can the conception of general conformation be said to be concrete, for much the same variations are found in both sexes.

#### PELVIC PLANES AND CONTOURS

When we consider the bony pelvis and, in particular, the birth canal, it is at once obvious that we are dealing with an intricate structure. Furthermore, inasmuch as the entire birth canal is involved in the process of birth, it must be studied obstetrically as a whole and not segmentally. This does not mean that a concept of certain planes and contours is not of essential use for purposes of description and for the estimation of pelvic capacity. For this purpose a simplification of the problem becomes possible by considering three portions of the pelvis; viz., the pelvic inlet, the pelvic outlet and the pelvic sidewalls. A consideration of these will furnish information which will be of distinct advantage in estimating pelvic capacity and in describing pelves (see Figs. 5 and 6).

#### THE PLANE OF THE PELVIC INLET

In considering the pelvic inlet, we describe this portion of the pelvis as follows:

From the obstetric point of view this plane is bounded anteriorly by the upper posterior surface of the symphysis and the forward portions of the iliopectineal lines, laterally by the iliopectineal lines and posteriorly by the posterior portions of these lines and the anterior upper surface of the sacrum at the point where the convergence of these lines takes place. (This point may or may not be located at the sacral promontory.) The essential diameters of this plane are:

1. *The anteroposterior diameter* extending from a point on the posterior surface of the symphysis, 1 cm. below its superior border, to the anterior surface of the upper sacrum at the point where the iliopectineal lines would meet were they to be extended.

2. *The transverse diameter* being the widest distance separating the iliopectineal lines.

3. *The posterior sagittal diameter*, which is that portion of the anteroposterior diameter which lies posterior to its point of intersection by the transverse diameter. The length of this diameter is a good index to the amount of space in the upper posterior pelvis and also gives some information as to the shape of the plane of the inlet, for when shortened it means a posterior displacement of the transverse diameter.

In considering the plane of pelvic inlet, as outlined, any abnormalities should be noted with regard to symmetry and to the configuration of its anterior and posterior segments. When the anterior segment is narrowed or angular, this fact may have definite obstetric significance.

## SUMMARY OF MANEUVERS FOR PELVIC ESTIMATION

Thus far we have spoken of eight diameters which we may consider as the *cardinal diameters of the pelvis* all of which may be measured satisfactorily by roentgen means. It is useful here to point out certain general information which we should also seek in the evaluation of pelvic capacity. A good deal of such information may be secured by manual examination and inspection of the patient. A consideration of the gait, general constitution, and shape of Michaelis' rhomboid is of value. By vaginal and rectal examination much can be learned if the observer keeps in mind the possibilities and limitations of these maneuvers. Palpation of the pubic arch, the determination of the downward course of the pubic rami, the width of the tubera ischii should be noted and recorded. Vaginal examination should include the palpation of the ischial spines, their relation to the anterior surface of the sacrum, and the course of the sacral curve from above downward. An attempt should be made to evaluate whether or not the pelvic sidewalls converge more than usual in the lower pelvic space. The determination of the diagonal conjugate as described in textbooks does not serve any useful purpose as long as roentgen pelvimetry is to be carried out. Indeed, I am convinced that, even when roentgen determinations are not done, the time-honored determination of the diagonal conjugate diameter in some instances actually may be misleading. This is because of the great variation in the position of the sacral promontory in its relation to the true pelvic inlet. (This fact should be remembered by those who advocate the determination of the diagonal conjugate diameter as a criterion for the performance of roentgen pelvimetry in the individual case.) The rectal examination for determining the relationship of the ischial spines to the lower sacrum is a useful and important maneuver. Both rectal and vaginal examinations are important adjuncts in determining pelvic capacity.

Let us now consider the application of roentgen techniques to the visualization and mensuration of the pelvis. For this purpose I recommend for routine purposes the taking of two flat films consisting of one view of the pelvic inlet looking down into the pelvic cavity, which is spoken of as the inlet view, and the other depicting the lateral aspect of the pelvis. Obviously, in individual cases because of abnormalities or for purposes of study during labor, other views may be useful, and in this latter instance stereoscopic views may serve a very useful purpose. For routine pelvimetry the two views of which I have spoken appear entirely adequate, for all of the cardinal diameters may be measured and all of the important pelvic aspects may be studied. The techniques used in placing the patient in position will be described later. The inlet and lateral views are both taken at a 36 in. target film distance. This distance is kept uniform for two very important reasons. (1) *If films are always produced under this condition, the relative size values in comparing films will always be more or less constant, and in studying the pelvis as a whole this fact is very useful.* (2) *By using a 36 in. target film distance distortion due to spread of rays is minimized.*

logically by myself, the average for 61 males was 101.9 mm. and that for 92 females, 88.8 mm. Schuman recommends external measurement with a caliper pelvimeter and subtracts from 1 to 2 cm. for the thickness of the soft parts. I find that this measurement may be readily and satisfactorily made roentgenologically on the lateral film by a technique to be described later.

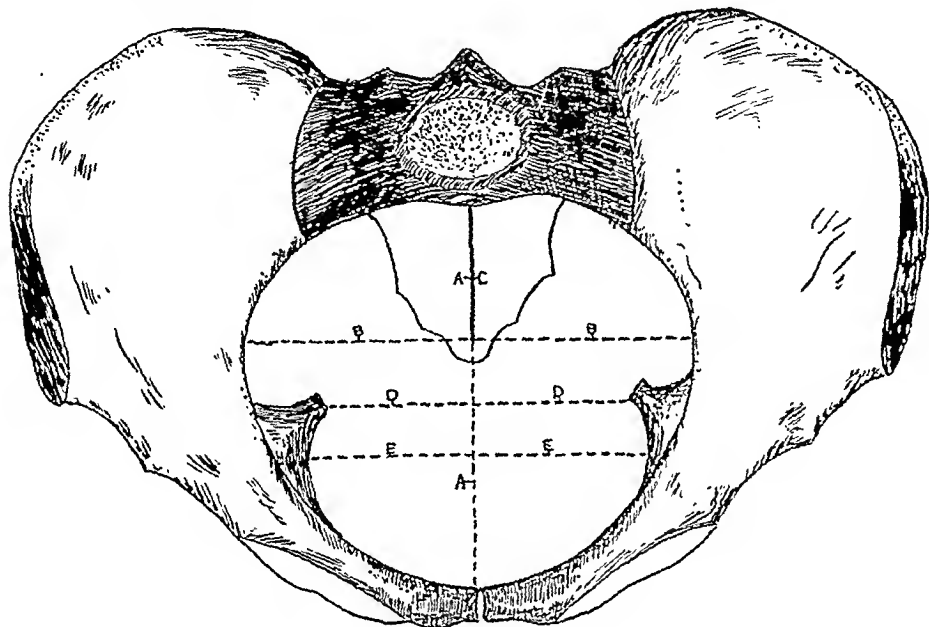


Fig. 5.—The pelvis as seen from above. The various diameters are shown. A, Anteroposterior diameter of inlet; B, transverse diameter of inlet; C, posterior sagittal diameter of inlet; D, bispinous or transverse diameter of midplane; E, widest transverse diameter of outlet.

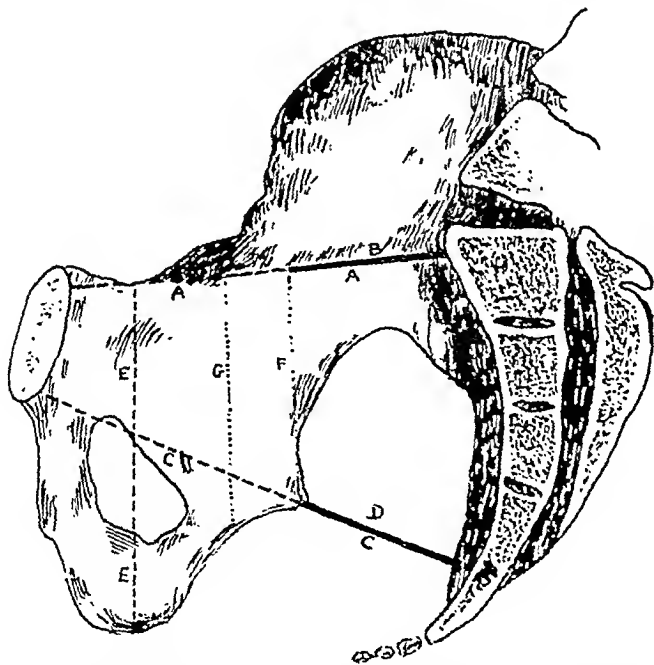


Fig. 6.—Lateral aspect of pelvis. Diameters and distances establishing levels are shown. A, Anteroposterior diameter of inlet; B, posterior sagittal diameter of inlet; C, anteroposterior diameter of midplane; D, posterior sagittal diameter of midplane; E, pubotuberous diameter; F, distance establishing level of ischial spines; G, distance establishing level of widest transverse diameter of outlet.



Our routine is to take the lateral projection first and this may be described as follows:

1. The patient removes her clothing, putting on heelless slippers and the usual hospital bed gown open at the back.

2. She is placed standing in front of an erect Bucky diaphragm or an adjustable cassette changer, such as is used for chest work, with either the right or left lateral aspect of the body toward the target. The arms are folded across the chest.

3. The target film distance is 36 inches and the target is centered just below a point on the external conjugate diameter one-third the distance from the symphysis pubis to the depression under the fifth lumbar vertebra.



Fig. 7.—Lateral roentgenogram. Compare with Fig. 6. The scale represents corrected centimeters in the midplane of the body. By means of calipers the various dimensions depicted in Fig. 6 may be measured. The lateral morphologic aspects are readily visualized.

4. A binder is placed around the patient and attached to the cassette changer to insure further steadiness during the exposure.

5. Before the exposure is made, an upright metal rod (lead and iron) with a centimeter scale perforated in a lead strip is placed posterior to the patient close to the fold of the nates.

6. The time of exposure varies with the thickness of the patient, all other factors being constant; in general the time is from seven to twelve seconds.

*Comment on Lateral Technique.*—When developed and viewed (Fig. 7) the following landmarks should be readily identified: anterior and posterior borders of the symphysis pubis, acetabula, ischial spines, ischial tuberosities, the lower lumbar vertebrae, the promontory and anterior surface of the sacrum, and the sacrosciatic notch. On one edge of the film may be seen the shadows cast by the perforations giving corrected centimeters in the sagittal plane of the patient. By means of calipers, using this scale, any diameters in this plane may be measured.

Having obtained an inlet view of the pelvis on a flat film, we should first study the bony pelvic relationships as a whole. The symmetry or asymmetry of the pelvis from above downward is readily determined. The general shape of the inlet is seen and the position of the pelvic side-walls, ischial spines, etc., are depicted with clarity. The various forms of pelvic variation and the presence of certain malelike characters become readily apparent in this view. In the lateral view we note the height of the pelvis, the curve of the sacrum, the character of the notch, the thickness and inclination of the symphysis and the position of the sacral promontory in its relation to the pelvic inlet. As in the inlet view the pelvis is studied, also, as a whole from this aspect. It is, however, important to take certain pelvic measurements to supplement this information and to further determine the capacity of the pelvis.

#### PELVIC MENSURATION

With regard to pelvic measurements per se it should be emphasized that, valuable as they are, they are by no means the sole criteria upon which obstetric prognosis should be based. Such determinations form the basis for a practical classification of pelvis and also are an important index of pelvic capacity. To those who think that pelvic measurements have but academic interest I would point out the truth of Lord Kelvin's dictum that, "When you can measure what you are speaking about and express it in numbers you know something about it, but when you cannot measure it, when you cannot express it in numbers your knowledge is of a meagre and unsatisfactory kind."

In making flat films of the pelvic inlet and the lateral pelvic aspect, it is clear that for purposes of proper mensuration, correction of the distortion due to the spread of the roentgen ray must be made. It is also obvious that if we can identify in space any plane to be measured and its position relative to the target, this distortion may be compensated for. This is done by means of the lead grid and upright rod to be described later.

As stated before, for routine pelvimetry we insist upon two views, one lateral and one pelvic inlet projection. Both views are necessary for the proper survey of the pelvis, and, furthermore, each view becomes an excellent check upon the other, as the anteroposterior diameter of the inlet may be measured in both.

#### ROENTGEN TECHNIQUE FOR ROUTINE PELVIMETRY

The technique which we are at present using has been recently described by H. M. Wilson and myself<sup>5</sup> and is here reprinted in detail. It represents a slight change in the lead grid from that which we have previously used, and this has been made in order that in the inlet view the transverse diameters of levels other than that of the pelvic inlet may be measured. However, in both these inlet and lateral techniques the fundamental principle remains unchanged.

posterior point on the body and the point on the upper and anterior surface of the symphysis will bisect the plane of the pelvic inlet. This line should be parallel to the film and this is brought about by adjusting the position of the patient so that the end points are equidistant from the table top.

3. The tube is centered in the midline about 6 cm. posterior to the upper border of the symphysis and the exposure is made.

4. The patient is removed from the table, the tube and exposed film remaining in situ.

5. The centimeter grid, a lead plate with perforations along one edge, is introduced into the same plane as that previously occupied by the pelvic inlet, as determined by the caliper readings, and a second (flash) exposure made on the edge of the previously exposed film. This is done after moving the target so that it rests directly over the perforations in the grid, still maintaining the 36 in. distance.

*Comment on Inlet Technique.*—In viewing the inlet film (Fig. 8) the pelvic inlet, ischial spines, and pelvic sidewalls of the outlet are readily seen. At the top edge of the film are the projected perforations of the grid representing corrected centimeters for the various levels in the pelvis. The line of corrected centimeters at the top represents the level of the pelvic inlet and this scale is used in measuring the anteroposterior, transverse, and posterior sagittal diameters of the inlet. The five rows of perforations which are seen below this level are those to be used for the 5, 6, 7, 8, and 9 cm. levels below the pelvic inlet. Thus, if we wish to measure the interspinous diameter on this film, we find the level at which they rest in the lateral film by measuring downward from the level of the pelvic inlet; if, for instance, this is 6 cm., then on the anteroposterior film we use the second or 6 cm. calibration for the determination. The same holds true for measuring the widest transverse diameter of the outlet. This level also is determined in the lateral film and the proper calibration is used on the anteroposterior film. (Note: In determining this level we use a point on the lateral film which is 1 cm. below the lower end of line [G] Fig. 6.)

#### THE CLASSIFICATION OF PELVIC VARIATIONS

The classification which we have used for a number of years is simple and readily comprehended. It is based upon the shape of the pelvic inlet and specifically upon the relation of the lengths of the anteroposterior and transverse diameters to each other. It is in effect a slight elaboration of Turner's original classification and is, therefore, an index to the tendencies of pelves to dolichopellism, platypellism, and the intermediate stages referred to before.

For practical purposes I do not feel that classifications based upon the subjective impressions of sex characteristics are essentially practical, especially when 10 or 12 classes may be divided into many subgroups. Furthermore, until further studies are made of male pelves in the living on a scale somewhat commensurate with those of female pelves, our knowledge of the male pelvis cannot be complete. As an instance of the importance of such further study I would call attention to the variations in male pelves which Greulich and myself found in our series.<sup>2</sup>

The advantages of this lateral technique may be summarized as follows:

1. All the anteroposterior diameters of the bony pelvis may be measured, including those of the pelvic inlet and midpelvis.
2. The level of the ischial spines and the level of the lower inner surface of the ischial tuberosities may be determined in this view.
3. The contours of the anterior surface of the sacrum may be studied, a matter of importance in the recognition of sacral abnormalities, especially those due to the influence of rickets.
4. When lateral roentgenograms are made at term or in labor, the relation of the presenting part to the superior strait may be studied with advantage.



Fig. 8.—Pelvic inlet roentgenogram. Compare with Fig. 5. The scale represents corrected centimeters for various levels of the pelvic canal. The top line is used for measuring the diameters of the inlet. The other levels are established on the lateral roentgenogram (see text). Pelvic morphology is readily established by viewing both lateral and inlet views.

A recent modification of the centimeter grid method for pelvic inlet pelvimetry may be described in its essentials as follows:

1. The patient is placed on the roentgenographic table in a semi-recumbent position which is maintained by a back rest. In placing the patient in position we endeavor to make the pelvic inlet horizontal.
2. The level of the pelvic inlet above the sensitive film is established as follows: (a) By means of calipers the vertical distance is measured from some point on the table top to a point on the anterior surface of the symphysis pubis 1 cm. below its superior border. (b) By means of calipers the distance is determined from the interspinous space between the fourth and fifth lumbar vertebrae, as determined by palpation, to the table top. For practical purposes, an imaginary line drawn between the

## DISTRIBUTION OF PELVIC TYPES

In our total series (1,100 white women), the distribution of the basic types was as follows:

Dolichopellic	type occurred 205 times, or 18.6 per cent
Mesatipellic	type occurred 505 times, or 45.9 per cent
Brachypellic	type occurred 354 times, or 32.2 per cent
Platypellic	type occurred 36 times, or 3.2 per cent

## ANALYSIS OF PELVIC DIAMETERS IN 500 WHITE WOMEN

In order to obtain some idea concerning the normal range of measurements, certain data in the series of 500 women in whom the pelvis has been more completely studied may be interesting. From what has been said previously concerning pelvic variation, it is obvious that such measurements would be best studied according to pelvic type; that is the dolicho-, mesati-, and brachypellic types should be dealt with separately. The platypellic type occurs so infrequently and so often shows definite pathology that it is not considered. In this group of 500 women, the type distribution was as follows:

Dolichopellic	type 113 instances or 22.6 per cent
Mesatipellic	type 233 instances or 46.6 per cent
Brachypellic	type 144 instances or 28.8 per cent
Platypellic	type 10 instances or 2.0 per cent

The mean values for the pelvic types are shown in Table I.

As stated before, the values for pelvic height and widest outlet diameter are based on a smaller series and are shown in Table II.

TABLE I

	INLET			MIDPLANE		
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.
Dolichopellic	12.59	11.92	4.97	12.55	9.83	5.14
Mesatipellic	11.86	12.38	4.63	12.31	10.30	5.07
Brachypellic	11.07	12.81	4.34	12.14	10.48	5.08

TABLE II

	PELVIC HEIGHT (92 Pelves)	WIDEST TRANSVERSE OUTLET DIAMETER (99 Pelves)
Dolichopellic	8.8 cm.	11.3 cm.
Mesatipellic	8.8 cm.	11.9 cm.
Brachypellic	8.9 cm.	12.0 cm.

An analysis of the group reveals that some of them have dimensions which deviate considerably from the norm. It is, therefore, convenient and useful to define a range of average, in order that the measurements in any individual case may be more properly evaluated.

For clinical study, therefore, a dimension may be regarded as average if it lies within the interquartile range, which is the middle half of all pelves arranged according to the size of the dimension being studied. Any dimension outside of this range could, therefore, be spoken of as "small" or "large," as the case may be (differences of less than 0.25 cm. being disregarded). The ranges of average found in these 500 pelves are shown in Table III.

Again it should be emphasized that the anteroposterior and transverse relationships of the pelvic inlet in general are an index to these relationships throughout the pelvis in the various pelvic types. This is, of course, not true of those pelves which are grossly deformed or which have been subjected to the severe influence of disease, such as rickets.

The following pelvic variations as shown by the inlet conformation may be classified as follows:

1. *Dolichopellic or elongated type*: (Fig. 1.) The anteroposterior diameter exceeds the transverse diameter.

2. *Mesatipellic or round type*: (Fig. 2.) The anteroposterior and transverse diameters are of equal length, or the transverse diameter exceeds the anteroposterior diameter by not more than 1 cm.

3. *Brachypellic or oval type*: (Fig. 3.) The transverse diameter exceeds the anteroposterior by more than 1 cm. and less than 3 cm.

4. *Platypellic or flat type*: (Fig. 4.) The transverse diameter exceeds the anteroposterior by 3 cm. or more.

It should be understood that these are considered as basic types simply for purposes of classification, and in the description of pelves not only are these terms used, but such observations as symmetry, character of notch, of pubic arch, and of anterior segment of inlet are also added for descriptive purposes.

#### MATERIAL USED IN STUDY OF PELVIC TYPES

In 1939<sup>6</sup> the author and his associates published the results of routine roentgen pelvimetry in 800 white primiparous women. In this series the first 600 had the pelvic inlet measurements only, and in the latter 200 the entire pelvis had been measured. At the present time I am able to add 300 to the latter group in which the whole pelvis has been surveyed roentgenologically. Pelvic inlet studies are thus available in 1,100 white women.

The material upon which these studies have been made consists of patients who have been delivered in the Obstetrical Wards of The New Haven Hospital. All of the patients are of the white race and for the greater part are from American and European stock, and born in this country. The group, therefore, is probably quite representative of the mixed population which is to be found along our northeastern seaboard. This series represents cases of primiparous women who were consecutively delivered at term during a five-year period. However, in such a consecutive series it is inevitable that each year a few primigravid patients enter our wards as emergency cases advanced in labor and are delivered without previous pelvic mensuration. Such instances, however, are comparatively infrequent and consist of less than 5 per cent of the entire series. In this series, also, I have considered only term births, because it is my opinion that in any study having to do with cephalopelvic relationships, premature births should be omitted. A birth weight of 2,500 Gm. as a criterion in this connection may seem low, but this figure is that which is generally accepted as a division between premature and term infants. Obviously the great majority of our patients delivered infants whose weight was well above this figure.

## LOW FORCEPS

As stated before, the indications for low forceps are in general so broad that analysis is not likely to be very significant. Nevertheless, the figures are interesting and may show trend. The occurrence was as follows in the 500 cases:

Dolichopellic type	113	pelvis low forceps	27 times or 23.8%
Mesatipellic type	233	pelvis low forceps	48 times or 20.6%
Brachypellic type	144	pelvis low forceps	23 times or 15.9%

In commenting upon this frequency of operation, it may be said that if the indications for low forceps were based upon pelvic conformation alone, this is what might be expected; that is, in the dolichopellic type with relatively convergent pelvic sidewalls and therefore relative transverse narrowing of outlet, the incidence of low forceps might be expected to be higher than in the brachypellic type where broadening of the outlet is a significant feature. Obviously, the incidence in the mesatipellic type would occupy a midposition. The figures show the incidence of low forceps to be one-third greater in the dolichopellic type than in the brachypellic.

#### FETAL AND MATERNAL MORTALITY IN THE SERIES OF 1,100 PRIMIPAROUS WHITE WOMEN DELIVERED AT TERM

In this series of 1,100 women there were no maternal deaths and 17 fetal deaths. Among the latter, there were 3 cases showing gross fetal abnormalities and three cases of ante-partum death resulting in the birth of a macerated fetus.

#### CONCERNING THE ETIOLOGY OF PELVIC VARIATIONS

In the consideration of these variations in pelvic architecture it is interesting to speculate concerning the etiologic factors which may be concerned in their production. The greatest changes from the fetal to the adult type of pelvic architecture occur at or near the time of puberty. This has been shown in the studies of Greulich and myself,<sup>7</sup> who have observed these changes in a single group of individuals by roentgenologic study over a period of years. The recent studies of the pelvis in male and female children by Morton and Hayden<sup>8</sup> also substantiate this opinion. A part of their summary follows: "These findings suggest that both males and females start out life with pelvis which are identical in type and that the major differences observed in adult male and female pelvis do not appear until puberty and are, therefore, due to the influence of the sex hormones." However, these authors also suggest that other factors than sex, such as nutrition and disease, probably play major roles. Some years ago I suggested that nutrition may play such a major role and stated the following: "The predominant type of pelvis which was formerly seen in clinics may have actually changed in character within a generation. When one considers alteration in environment surrounding female infants and adolescent children during the past twenty-five years, changes brought about not only by a great difference in diet, but by such influences as outdoor life and life in the open, it must be admitted that the environment for this group has

TABLE III

	DOLICHOPELLIC	MESATIPPELLIC	BRACHYPELLIC
<i>Inlet</i>			
Anteroposterior	12.0 -13.0	11.5 -12.25	10.5 -11.5
Transverse	11.5 -12.25	12.0 -12.75	12.25-13.25
Posterior sagittal	4.5 - 5.5	4.25- 5.0	4.0 - 4.5
<i>Midplane</i>			
Anteroposterior	12.0 -13.0	11.75-13.0	11.5 -12.75
Transverse	9.25-10.25	10.0 -10.75	10.0 -11.0
Posterior sagittal	4.75- 5.5	4.5 - 5.5	4.5 - 5.5

If we wish to consider the pelvis as a whole in reference to its being small, average or large, it is my opinion that the anteroposterior diameter of the inlet may be used as a criterion for such classification since it appears to be the most important single dimension. Using this diameter as a yardstick, therefore, it appears that we may designate "small" pelvis in the various types as follows:

Dolichopellic type A. P. Diam. less than 12.0 cm.  
 Mesatipellic type A. P. Diam. less than 11.5 cm.  
 Brachypellic type A. P. Diam. less than 10.5 cm.

#### OPERATIVE INTERVENTION IN 500 WHITE WOMEN

In considering operative intervention per se in its relation to pelvic conformation in the series (500 pelvis) a truer picture of the situation is seen if we omit the consideration of low or outlet forceps. The reason for this is that in the primiparous woman the indications for this usually simple procedure are too broad for simple analysis. Breech extraction, because of breech presentation is also not considered.

In this group of 500 white patients, labor was terminated by operative intervention according to the above definition 33 times or in 6.6 per cent of cases. It is interesting to group such procedures according to pelvic type as follows:

*Dolichopellic Group:* 113 pelvis, 6 operations or 5.3 per cent of 113 labors.

*Mesatipellic Group:* 233 pelvis, 8 operations, or 3.4 per cent of 233 labors.

*Brachypellic Group:* 144 pelvis, 19 operations or 13.2 per cent of 144 labors.

*Platypellic Group:* 10 pelvis, 1 operation or 10.0 per cent of 10 labors.

If we separate these operations into those which were done chiefly or solely because of the presence of abnormal pelvic conformation, we find the following:

Dolichopellic type, 113 cases, 3 operations or 2.6 per cent.

Mesatipellic type, 233 cases, 1 operation or 0.4 per cent.

Brachypellic type, 144 cases, 11 operations or 7.6 per cent.

Platypellic type, 10 cases, 1 operation or 10 per cent.

These latter figures re-emphasize a previous statement that the most favorable type of pelvis for successful childbearing is one whose inlet is essentially round (mesatipellic) and not the transversely oval pelvis (brachypellic or platypellic).



expresses itself in one of its functions by tending to prevent undue softness of bone, which in itself may result from certain mineral imbalance occurring during the early puberal epoch, a period of relatively rapid skeletal growth.

#### ROENTGEN PELVIMETRY AS A ROUTINE PROCEDURE

After a period of nearly six years in which all primigravid women in our prenatal clinic have had roentgen pelvimetry, it might be well to consider such a routine in the light of its value as a clinical procedure. I think most observers will agree at the present time that external pelvimetry is of but little use in determining actual pelvic capacity, and for a comparative study by the author on this subject, reference is here given.<sup>13</sup> It seems clear that if pelvimetry is a valuable procedure at all, we must have accurate observations. In the living woman it is impossible to secure such data except by means of roentgen techniques.

It is, of course, evident that most women have pelves which are adequate for the delivery of most babies, but scientific obstetrics cannot be conducted on any such philosophy, for applied to the individual case it is obviously fraught with danger. Most obstetricians of experience will recall instances where an unsuspected midplane contraction or other pelvic abnormality was responsible for an unlooked for difficult forceps operation, often accompanied with the loss of the baby. The routine use of antenatal roentgen pelvimetry should and does anticipate many of such difficulties. Not infrequently I have seen patients who from all other evidence seem to possess adequate pelves and yet have found upon roentgen examination some restriction of capacity in one or more of the important pelvic planes. This does not mean that such patients were treated radically, but it does mean that in many instances treatment was modified to suit a situation which was well understood.

It does not appear that routine roentgen studies tend to radicalism in obstetric procedure. Our figures for major obstetric operations in these 1,100 primiparas are as follows:

Cesarean section	26 times, or 2.3%
Version and extraction	5 times, or 0.4%
Midforceps	39 times, or 3.5%

Furthermore, it is obvious that some of these operations were done for other than difficulties associated with pelvic conformation.

In discussing the routine use of these roentgenographic procedures, it should be re-emphasized that the use of two views on flat films as described is not only entirely adequate for such a pelvimetric survey, but also renders the cost of the procedure well within the limits of most of the usual laboratory techniques. On our ward service in which teaching is carried out, the films of each primigravida are made available as soon as the patient enters the hospital for delivery. At this time the morphologic aspects of the pelvis are again reviewed by those attendant upon the delivery. In addition, the prenatal record is consulted concerning the pelvic dimensions. An observation concerning routine pelvimetry which has been of interest to me is the fact of its reception and adaptation to private practice by many of the obstetricians practicing

changed indeed during that period. When one further considers the sedentary habits, the type of clothing, the diet, and general restrictions that previously were a part of the life of female infants and children, may one not speculate as to the effect of such an environment on the adult form of the female pelvis. That changes in environment can effect skeletal changes in a large population is witnessed in recent years by the extraordinary lessening of the incidence in children of severe rachitis.<sup>79</sup> In surveying the results of Greulich and myself in studies in women of the college group, as contrasted with those of the clinic group, it would appear that environment during the growth period was a factor in the lessening of the number of the brachy- and platypellie types of pelvis found in the former group.

For purposes of emphasis I repeat a portion of one of our tabulations here:

	104 STUDENT NURSES	582 CLINIC WOMEN
Dolichopellic	37.5%	15.0%
Mesatipellic	44.2%	44.8%
Brachypellic	18.2%	34.3%
Platypellic	-	5.6%

It seems probable that, as far as variations of the pelvis are concerned, both nutritional and hormonal influences play major roles, and it may indeed be that one of the effects of increased hormonal activity at the time of puberty is to preserve the general fetal conformation (dolichopellism). The evidence for this statement is not overwhelming, but there is some evidence for its consideration.

In a recent study in mental and physical growth in pubertas precox made by Gesell, Thoms, Hartman, and Thompson,<sup>10</sup> the findings in a girl who had been under observation for fifteen years formed the basis of the report. The child at the age of three and one-half years underwent all the phenomena of puberty including menstruation. In this instance, therefore, the hormonal influence may be said to have been abnormal, an influence extending over a relatively long period of years and which, therefore, might give some suggestion of its influence on the formation of the adult pelvis. The findings at the age of seventeen are of considerable interest. At that time she presented a typical dolichopellic type pelvis; anteroposterior diameter of inlet 12.0 cm., transverse 11.25 cm., all of the other diameters and contours of the pelvis corresponded to what we consider as the typical elongated or dolichopellic type.

Other evidence that the sex hormones may have a definite influence on bone formation is found in the interesting report of Hills and Weinberg<sup>11</sup> on the influence of estrin on callous formation. They report three cases of fracture with delayed union which were treated with estrogenic hormone with resultant signs of increased callous formation. Interesting also are the findings of Pfeiffer and Gardner,<sup>12</sup> who found that in pigeons the administration of estrogenic substances during ovulation produced an increased density of bone.

From such evidence as the above it may be permissible to conjecture that the incidence of the increased secretion of sex hormone at puberty

# EXTRACELLULAR WATER IN LATE PREGNANCY AND ITS RELATION TO THE DEVELOPMENT OF TOXEMIA

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MANY writers have regarded excessive or rapid weight gain in late pregnancy as a premonitory sign of impending toxemia, and have established that the incidence of toxemia is increased in those women who gain too much or too rapidly. Such weight gains do not always precede toxemia, and not all women gaining excessively do develop toxemia. In many of those women who do become toxic, part of the excessive or rapid weight gain presumably represents the accumulation of edema water. Others may add fat or protoplasm. It would be interesting to separate the water-gainers from the protoplasm-gainers, and to compare the incidence of toxemia in the two groups. Possibly such a separation might have a practical value in the detection of developing toxemia.

In the present study we have attempted a differentiation between women accumulating water and those gaining protoplasm, by measuring the "available water" for thiocyanate distribution. This measurement is thought to give an approximation to the extracellular water of the body. We realize that the water gained in pregnancy and in toxemia may not be wholly extracellular.

The principle of the test is simple. Equation of "available" water with extracellular water depends upon 2 assumptions, neither of which is wholly valid. The assumptions are: (1) injected or ingested thiocyanate does not enter cells of the body, and (2) the thiocyanate attains the same concentration in all body water outside of the cells, so that the plasma concentration is the same as that in the interstitial fluids. As for the first assumption, thiocyanate does enter the red blood cells (Crandall and Anderson<sup>1</sup>), though these corpuscles are not typical cells; thiocyanate may also enter the salivary glands and pancreas. In the second place, there is usually a difference of about 10 per cent in the concentrations of thiocyanate in plasma and in edema fluid (Lavietes, Bourdillon and Klinghoffer<sup>2</sup>).

The procedure is: (1) inject an accurately known amount of thiocyanate, (2) allow a period of several hours for a uniform distribution of the salt, (3) measure the urinary loss of thiocyanate during the equilibration period, (4) determine the plasma (or serum) concentration of thiocyanate after equilibration, and (5) calculate the volume of "available" water by dividing the plasma concentration into the quantity of thiocyanate remaining in the body.

in my community. It is their feeling, as well as that of the members of our staff, that such a roentgen survey of the pelvis in the primigravid woman offers many distinct advantages and no disadvantages. Furthermore, this group have found these flat films of ready interpretation and have not of necessity had recourse to the opinion of the roentgenologist, or of one specially skilled in film interpretation. In this connection it should be emphasized that this bears out what the author has stated on previous occasions; namely, that the roentgenologist should not be expected to furnish opinion regarding prognosis in the clinical problems of a field where his experience obviously may be limited.

In discussing the routine use of roentgen pelvimetry in the primigravid patient, we should mention its great value in patients with borderline pelvis and in the primigravid woman with a breech presentation. In the latter situation it seems quite clear that in most instances one who attempts to deliver such a presentation without a knowledge of pelvic conformation and certain pelvic dimensions is not practicing modern scientific obstetrics. With regard to the borderline pelvis, not only is the information with regard to pelvic capacity useful, but views taken during labor may be of signal value in noting the progress of the labor. Mention should also be made of the value of roentgen studies in estimating fetal size and maturity, and reference to the author's work in that field is here given.<sup>14-16</sup>

In conclusion, it is interesting to recall these words of wisdom written in 1886 by an American physician, Dr. Henry Morris,<sup>17</sup> "It has been said that since the world began no two women have had pelvis which exactly resembled each other in every particular; that in each case there has been some difference more or less minute, by which any pelvis can be distinguished from all others. While this is probably an exaggeration, it is nevertheless true that the female pelvis is subject to many variations, both as regards its size and its shape. The 'normal pelvis,' therefore, is more of an ideal than of a reality—a pelvis conceived from the 'good points' of many pelvis, whose diameters are arrived at from averages derived from the measurements of thousands of specimens."

I wish to express my appreciation of the interest and assistance in these studies of Dr. Hugh M. Wilson and his associates of the Department of Roentgenology, Yale University. I am also deeply grateful to Dr. Irving Friedman for assistance in the preparation of certain statistical material.

#### REFERENCES

- (1) Greulich, W. W., Thoms, H., and Twaddle, R. C.: J. A. M. A. 112: 485, 1939.
- (2) Thoms, H., and Greulich, W. W.: AM. J. OBST. & GYNEC. 39: 56, 1940. (3) Caldwell, W. E., Moloy, H. C., and D'Esopo, D. A.: Ibid. 30: 763, 1935. (4) Schuman, W.: Ibid. 28: 497, 1934. (5) Thoms, H., and Wilson, H. M.: Yale J. Biol. & Med. 13: 831, 1941. (6) Thoms, H., Foote, W. R., and Friedman, I.: AM. J. OBST. & GYNEC. 38: 634, 1939. (7) Greulich, W. W., and Thoms, H.: Anat. Rec. 76: Suppl. 2, 26, 1940. (8) Morton, D. G., and Hayden, C. T.: AM. J. OBST. & GYNEC. 41: 485, 1941. (9) Thoms, H.: Ibid. 31: 111, 1936. (10) Gessel, A., Thoms, H., Hartman, F. B., and Thompson, H.: Arch. Neurol. & Psychiat. 41: 755, 1939. (11) Hills, R. G., and Weinberg, J. A.: Bull. Johns Hopkins Hosp. 68: 238, 1941. (12) Pfeiffer, C. A., and Gardner, W. U.: Endocrinology 23: 485, 1938. (13) Thoms, H.: AM. J. OBST. & GYNEC. 27: 270, 1934. (14) Idem: Ibid. 20: 807, 1930. (15) Idem: J. A. M. A. 95: 21, 1930. (16) Idem: AM. J. OBST. & GYNEC. 29: 876, 1935. (17) Morris, H.: Science and Art of Obstetrics (Parvin, T.) Philadelphia, 1886, p. 473, Lea Bros. & Co.

fied. Further study, now in progress, will perhaps give a more definite answer. (Incidentally, the curves were tentatively drawn by the first criterion before the outcomes of the pregnancies were known.) Whatever the form of the curve, the data clearly demonstrate a marked difference between light-weight and heavy-weight patients, which must be considered in any interpretation of measurements of the available water in pregnancy.

The only publication in which there is any suggestion that the proportion of available water to body weight may vary with the weight, in nonpregnant individuals, is that of Brodie, Brand, and Leshin<sup>4</sup> who

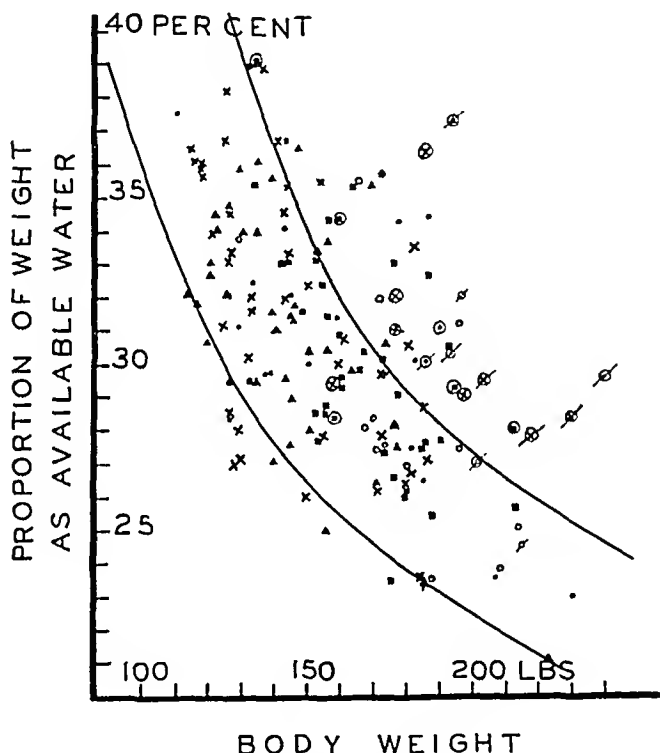


Fig. 1.—The relation between body weight and the proportion of the weight represented by available water. All cases are shown. The weight gains in pregnancy are denoted as follows: Less than 10 pounds ●; 11 to 20 pounds ×; 21 to 30 pounds ▲; 31 to 40 pounds □; 41 to 50 pounds ○; more than 51 pounds p. Circled symbols indicate patients developing toxemia of pregnancy subsequent to the measurement of available water. Circled symbol with cross-stroke indicates borderline toxemia as described in text. Further work indicates that the descending limbs of the curves perhaps are too steep and that no patient should show available water amounting to more than about 37 per cent of the body weight.

report on 6 cases. In other papers, few cases have been studied and most of the body weights have been nearly average. Crandall and Anderson<sup>1</sup> measured the available water in 3 nonpregnant women, and Stewart and Rourke<sup>5</sup> have recently recorded data for 19 normal women. These data have been re-calculated and plotted in Fig. 2, in the same manner as the data for pregnant women were plotted in Fig. 1. While it is hazardous to draw curves for these few points, there does appear to be some correlation between the body weight and the proportion of available water; this correlation appears grossly to be similar to that plotted for pregnant women.

## MATERIAL

We selected from the ante-partum clinic 180 patients who manifested no signs or symptoms of toxemia, other than excessive weight gain in some cases. These women were in their last six weeks of pregnancy. Each patient was given intravenously 20 ml. of 5 per cent sodium thiocyanate (Abbott's sulfoeyanate), and asked to come back the following day bringing with her all urine passed in the interim. Thus there was a period of eighteen to twenty-four hours (usually twenty-one hours) for the thiocyanate equilibration. When the patient returned, a blood sample was taken, and the urine collection was completed.

Thiocyanate was determined in modified Folin-Wu filtrates of serum and urine. The Evelyn photoelectric colorimeter was used for the measurement of the color developed by the addition of an acid solution of ferric nitrate. The method has been described elsewhere (Chesley<sup>3</sup>).

The completeness of the urine collections was checked by determination of the creatinine excretion. In the few cases in which large volumes of urine had obviously been lost, the test was not recorded.

The "available" water was calculated in terms of percentage of the body weight. Surface area calculations were not made, because it was thought that the usual formulas do not obtain in late pregnancy.

In many patients the measurement of available water was repeated on the third to ninth (usually sixth) day after delivery. When the test was repeated, a "blank" blood sample was first taken, in order to correct for any residual thiocyanate from the first test. The thiocyanate was then given by mouth, and twenty hours were allowed for equilibration.

## RESULTS AND DISCUSSION

*Normal Pregnancy.*—Toward the end of normal pregnancy the proportion of available water to body weight varies greatly, the proportion depending chiefly upon the body weight. In women weighing more than 200 pounds, the normal proportion of available water is about the same as that usually alleged for nonpregnant women, i.e., 20 to 26 per cent. But in women weighing less than 120 pounds the normal proportion of available water is much higher, 33 to as much as 37 per cent of the subject's weight. If we accept without reinterpretation the published data for nonpregnant women, normal pregnancy would seem to double the available water in light-weight women without adding much to the heavy-weight patients. This does not seem reasonable, and a reinterpretation of published data for nonpregnant individuals will be offered presently.

All data for pregnant women are represented in Fig. 1. The lines were drawn arbitrarily in an effort to define the normal proportion of available water in relation to body weight. If we exclude the patients who developed hypertensive toxemia subsequent to the measurement, the upper line includes over 85 per cent of all cases. The normal limits are represented as curves for three reasons: (1) such curves seem, by inspection, to fit the general trend of the points. (2) most of the pre-toxic patients are thus relegated to the "abnormal" area, and (3) the patients thus separated as "abnormal" lose much larger quantities of available water after delivery. Whether these are valid and acceptable criteria remains to be seen. In the present series of 180 cases such arbitrary delimitation of the normal range of available fluid seems to be justifi-

lations of available water, in nonpregnant individuals, from the serum concentrations of thiocyanate at four, eight, and twenty-four hours after injection of thiocyanate are in close agreement, which at least rules out the *progressive* binding or intracellular loss of thiocyanate.)

In pregnancy, even the twenty-one-hour period which we have allowed is not sufficient for an even distribution of thiocyanate if we consider the amniotic fluid as extracellular water. For at the end of twenty-one hours the concentration of thiocyanate in amniotic fluid is only about one-half that in serum. After thirty-six hours the concentration in amniotic fluid is still but two-thirds of that in serum. Our measurements of available water, then, include about half of the amniotic fluid. Presumably it also includes the extracellular water of the fetus.

*Pretoxic Patients.*—When the measurements of available water were made, no patient manifested hypertension, proteinuria, or any other sign of toxemia of pregnancy, except possibly abnormal weight gain in some cases. Clinically the pretoxic patients could not be separated from those who were to complete their pregnancies without toxemia.

As Fig. 1 shows, most of the patients who did become toxic had already gained excess available water at the time of the test. However two (possibly three) cases of toxemia did appear among those patients having normal proportions of available water at the time of the test. In one of these women, the determination of available water was made six weeks before the first elevation in blood pressure; possibly she had accumulated water in the interim. The second patient showed mild elevations of the blood pressure within a week of the time at which we found a normal proportion of available water, and therefore the conventional signs of toxemia apparently were not preceded by extracellular water retention. A third patient coming within the normal area showed a mild hypertension first appearing on the third day post partum; no other signs or symptoms of toxemia were manifest.

If we divide all patients into two groups, the one comprising patients with normal proportions of available water and the other those with excessive water, we find a remarkable difference in the incidence of toxemia. Among 141 patients with normal proportions of available water, 2 (or 3) developed hypertensive toxemia (mild pre-eclampsia), an incidence of 1.42 (or 2.13) per cent. In the 39 patients having excessive water, 9 became unquestionably toxic, and an additional 7 showed borderline blood pressures (near 140/90) before or after delivery. Four of these patients had only a post-partum hypertension. Thus the incidence of pre-eclampsia with hypertension is at least 23.1 per cent. If the borderline cases all be included, and certainly they were not strictly normal, the incidence of toxemia would be 41.0 per cent.

In brief, it would seem that a high proportion of pre-eclamptic patients accumulate extracellular water in abnormal amounts before hypertension, proteinuria, or (often) excessive weight gain becomes evident. Not all patients showing such abnormal water retention, however, will later develop the signs and symptoms of pre-eclampsia. Since most of

If curves approaching the form of those drawn in Fig. 2 actually do describe the relation between body weight and the proportion of available water, then the data in Fig. 1, for pregnant women, become more comprehensible. We need no longer consider that pregnancy doubles the available water of the 100-pound woman and adds no water in the 200-pound subject, but rather that pregnancy merely shifts upward the curve for all pregnant women.

(The data of Stewart and Rourke<sup>3</sup> fall considerably below the volumes found by other investigators. The reason for this is very probably the fact that Stewart and Rourke<sup>5</sup> base their calculations upon the serum thiocyanate concentrations as determined at thirty to forty minutes after

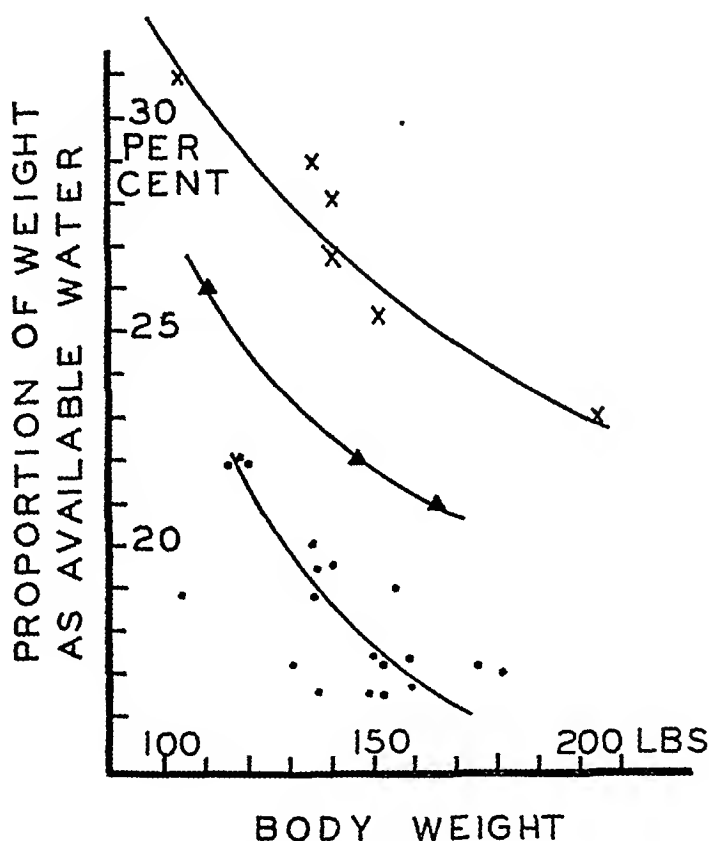


Fig. 2.—Published data of other writers, for available water in nonpregnant adults. Data of Brodie, Brand and Leshin (X) for men, using bromide method. Data of Crandall and Anderson (▲) and of Stewart and Rourke (●) for women, using thiocyanate method.

the injection of the thiocyanate. It has been shown by Goudsmit, Louis, and Scott,<sup>6</sup> and by Gilligan and Altschule<sup>7</sup> that the calculated volume of available water is considerably lower at this time than are the volumes calculated from serum concentrations determined some hours later. Perhaps the thiocyanate does not become distributed uniformly in extracellular water within half an hour, and the calculated volume of available water is too low. Or perhaps with longer equilibration periods some thiocyanate enters certain cells or is bound in some manner, thus giving falsely high values for the available water. The latter possibility would seem improbable from observations made by several writers: the calcu-



of the data leads to the conclusion that the available water measurements are more reliable than total weight gain in picking out potential toxemia patients.

When we consider rapid weight gains, we again find that many pre-toxemic patients do not show any abnormality. In the first place, rapid weight gain is very frequently absent in developing toxemia. For instance, in a series of 236 pre-eclamptic cases occurring in 1935 and 1936, rapid weight gain (more than  $1\frac{1}{2}$  pounds per week) preceded hypertension in only 22.9 per cent of cases. (No account has been taken of rapid weight gain after the appearance of hypertension.) Second, the majority of patients with excessive available fluid had not shown rapid weight gain at the time of the test.

#### LOSS OF AVAILABLE WATER IN DELIVERY AND EARLY PUERPERIUM

We have not made a systematic study of the extracellular water just before and just after delivery, but in 52 cases the measurement of available water was repeated post partum. The original determination was made anywhere from one day to as much as five weeks before delivery,

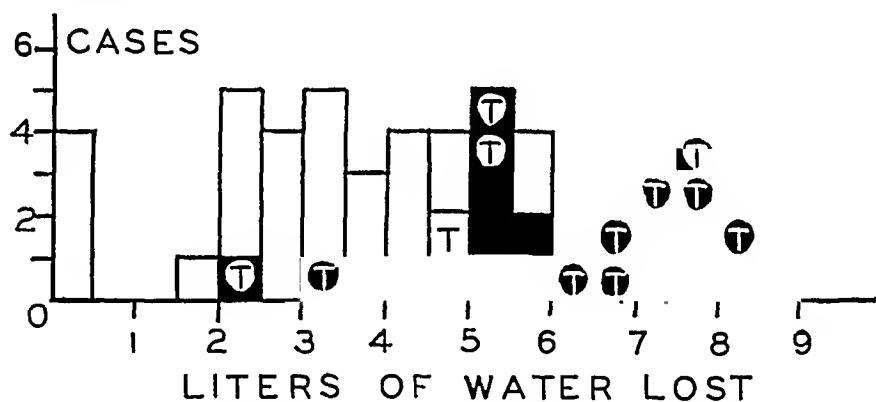


Fig. 4.—The loss of available water from the time of the ante-partum measurement until the sixth day (average) post partum. Patients grouped in the normal area of Fig. 1. □ Patients grouped in abnormal area of Fig. 1, denoting excessive available water ■. Patients developing toxemia are indicated by 'T'.

while the repetition was usually made on the fourth to sixth day post-partum. Thus many of the patients gained or lost unknown volumes of extracellular water between measurements, and the data have little quantitative value.

These measurements of available water, made post partum, do have some value, in that they demonstrate that those patients coming within the "abnormal" area in Fig. 1 are the individuals who lose the most water between the times of the first determination and the post-partum repetition of the test. In Fig. 4 we have plotted the frequency distribution of these water losses, and indicated which patients had come within the abnormal area, and which ones developed pre-eclampsia. Of the 39 patients who had excessive available water at the time of the antepartum test, 25 had rechecks; 80 per cent of these lost unusually large amounts of available water between tests.

the patients in this group were put on a diet restricting salt, water, and calories, it is conceivable that the development of pre-eclampsia was modified or even aborted.

Toxemia of pregnancy remains essentially undefined. We are learning more and more of its signs and symptoms, and by routinely taking blood pressures in pregnant women, we are today diagnosing toxemia in patients who would otherwise, and in another time, have been considered normal. Hypertension is not universally present in toxemia, nor is its presence a *sine qua non* for the diagnosis of toxemia. This might be emphasized by citation of statistics on eclampsia. In a series of 215 eclamptic patients, the systolic blood pressure was consistently less than 150 mm. Hg in 84, or 39 per cent of all cases. In about 12 per cent the systolic pressure was less than 140 mm. Hg whenever measured. Hypertension is merely a sign, and possibly a late sign, of some fundamental disturbance, the nature of which is unknown. Perhaps water retention is an earlier and even a more general sign of the disturbance which we call toxemia.

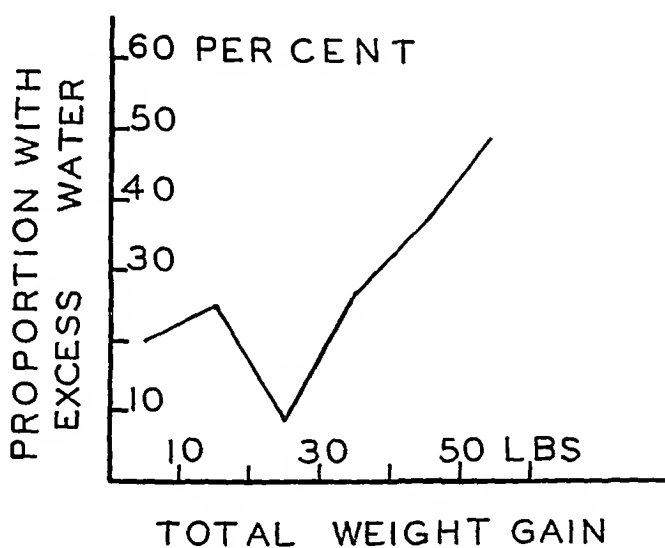


Fig. 3.—The relation between excessive weight gain and excessive water gain in late pregnancy. Most patients with excessive weights gains do not have excessive available water, and do not develop toxemia.

#### RELATION OF WEIGHT GAIN TO EXTRACELLULAR WATER

It is a common clinical practice to weigh the pregnant patient regularly, because edema formation may often be revealed by the excessive or rapid weight gain. It is interesting, therefore, to compare the weight gain with the measurements of extracellular water. Reference to Fig. 3 will show that there is some correlation between the total weight gain and the proportion of available water. Yet in the 2 patients gaining more than 60 pounds, the proportions of available water were perfectly normal, indicating that these women had gained protoplasm. On the other hand, half of the women having too much available water had had normal total weight gains (less than 20 pounds). A consideration

The component parts of the ovary, aside from the ovum are:

1. The granulosa cells
2. The theca interna
3. The stroma of the ovary
4. The vascular bed
5. The corpus atreticum

Stimulation of the ovary by the anterior pituitary will depend on the quality, quantity, and admixture of the various gonadotropic factors of the hypophysis as well as the sensitivity and receptiveness of the various components of the ovary. Any disturbance in this intricate and delicate mechanism may cause an imbalance with consequent sequelae that will effect not only the anterior pituitary-gonad balance but also distant organs as the uterus, endometrium, genital tract, and breasts that depend on balanced sterol production.

It has been well established that the ovaries of experimental animals react in different ways to the various gonadotropic factors.

For instance, Engle<sup>3</sup> has shown that the immature mouse ovary responds to extracts of pregnancy urine by exhibiting follicle atresia, luteinized follicles, and no ovulation, but responds to extracts of the anterior pituitary by follicle stimulation and ovulation. In the human being, the consensus has been that anterior pituitary-like substances fail to stimulate the ovary to produce follicle maturation, ovulation, and corpus luteum formation (Geist,<sup>4</sup> Hamblen and Ross<sup>5</sup>). The recent work of Davis and Koff,<sup>6</sup> and Siegler and Fein<sup>7</sup> tends to show that such stimulation may be obtained by the use of pregnant mares' serum. In previous communications, we have maintained that neither anterior pituitary extracts, nor equine, nor chorionic gonadotropins were capable of producing orderly maturation of follicles, ovulation, and corpus luteum formation in patients with nonreceptive or subnormal ovaries (primary ovarian insufficiency). However, in patients with normal ovaries, the normal processes may be augmented or even duplicated.<sup>8, 9</sup> Hartman<sup>10</sup> has shown that in the rhesus monkey, though ovulation could be induced, there was no guarantee that an endocrine condition favorable to the implantation of a fertilized ovum existed.

The purpose of this communication is to point out that the various gonadotropins undeniably are capable of stimulating the human ovary. What is the nature of this stimulation as seen histologically in the normal and subnormal ovary? Though ovulation cannot be induced in certain subnormal ovaries, nevertheless certain components of the ovary are responsive which may account for the clinical improvement seen in certain cases of oligomenorrhea, amenorrhea, menorrhagia, dysmenorrhea, etc.

#### HISTOLOGIC CONSIDERATIONS

A. *Ovarian Stroma*.—The stroma of the ovary is as much a gland of internal secretion as is the follicular apparatus. In various experimental animals the part played by the stroma cells is more clearly defined. The stroma may be influenced directly by the anterior pituitary or by its contiguity to active granulosa cells. The latter fact is clearly brought to point in the examination of granulosa cell tumors.

## SUMMARY AND CONCLUSIONS

We have measured the body water available for thiocyanate distribution (extracellular water) in 180 normal women in the last six weeks of pregnancy.

A curvilinear relationship is found between the body weight and the proportion of body weight represented by available water. On the basis of the few published data, it is suggested that a similar relationship exists in nonpregnant women.

Patients who are found to have excessive available water, although apparently normal otherwise, are prone to develop the classical signs and symptoms of pre-eclampsia. Pre-eclampsia very seldom appears in those patients having normal proportions of available water in late pregnancy.

Measurement of available water affords a more reliable index to the danger of developing toxemia than does weight taking.

Patients who have excessive extracellular water in pregnancy will have lost large amounts of this water by the sixth post-partum day.

We wish to take this opportunity to thank Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters for reading and criticizing the typescript.

## REFERENCES

- (1) Crandall, L. A., and Anderson, M. X.: *Am. J. Digest. Dis. & Nutrition* 1: 126, 1934. (2) Lavietes, P. H., Bourdillon, J., and Klinghoffer, K. A.: *J. Clin. Investigation* 15: 261, 1936. (3) Chesley, L. C.: *J. Biol. Chem.* 140: 135, 1941. (4) Brodie, B. B., Brand, E., and Leshin, S.: *Ibid.* 130: 555, 1939. (5) Stewart, J. D., and Rourke, G. M.: *J. Lab. & Clin. Med.* 26: 1383, 1941. (6) Goudsmit, A., Louis, L., and Scott, J. C.: *Am. J. Physiol.* 133: 297, 1941. (7) Gilligan, D. R., and Altschule, M. D.: *J. Clin. Investigation* 18: 501, 1939.

## HISTOLOGIC CHANGES IN THE OVARY FOLLOWING GONADOTROPIN ADMINISTRATION\*

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## INTRODUCTION

THE interrelationship of the anterior pituitary and the gonads was first demonstrated by Zondek and Aschheim,<sup>1</sup> Smith and Engle<sup>2</sup> in 1927. The utter dependency of the gonads on the anterior pituitary is readily appreciated. Less understood, however, is the controlling influence exerted by the gonads on the hypophysis. On first thought it might seem that the main concern of the anterior pituitary-gonad relationship is the maturation of the Graafian follicle, the expulsion of the egg, and the formation of the corpus luteum. Such a conception fails to take into account the component parts of the ovary that are subject to stimulation and play a role in the anterior pituitary-gonad complex.

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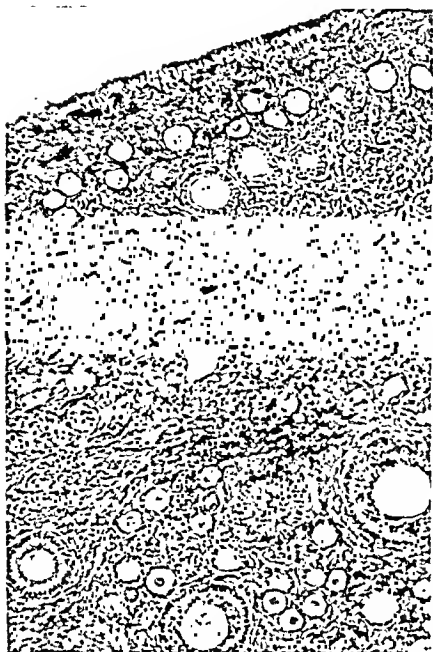


Fig. 2.



Fig. 3.

Fig. 2.—Note the polyhedral lipochrome cells in the juxtamedullary region of the ovary of a rabbit following the administration of 150 units of chorionic gonadotropin (pranturon) for three days with laparotomy on the fourth day. Note how they resemble interstitial cells of the testes.

Fig. 3.—Note that all the stroma of the rabbit ovary except the cortex, the granulosa cells of the follicle with its surrounding theca have been transformed into a lipid containing interstitium following the administration of 1 mg. of stilbestrol (synestrol), for four days, laparotomy on fifth day.



Fig. 4.—Note the patches at (A) of hypertrophied, vacuolated stroma cells in the cortex of the ovary. These, in a measure, resemble the paralutein cells of the corpus luteum which are visible at (B). Section from a human ovary following repeated doses of pregnant mares' serum for several months. (Sections by courtesy of Dr. Karl Karnaky.)

The connective tissue surrounding focal masses of granulosa cells frequently shows heavy deposition of lipoids<sup>11</sup> (Fig. 1). In the rabbit ovary, polyhedral lipochrome cells are occasionally seen in the juxta-medullary region, particularly after small doses of gonadotropins (Fig. 2). These resemble the Leydig cells seen in the testes. Under certain conditions these stroma interstitial cells are so stimulated that all the stroma of the rabbit ovary is transformed into lipid containing interstitium except for the granulosa cells and the surrounding thecal stroma (Fig. 3). This would tend to show that the interstitium of the rabbit ovary is not the same as the theca interna for both may respond to different stimuli although frequently responding to the same stimulus.

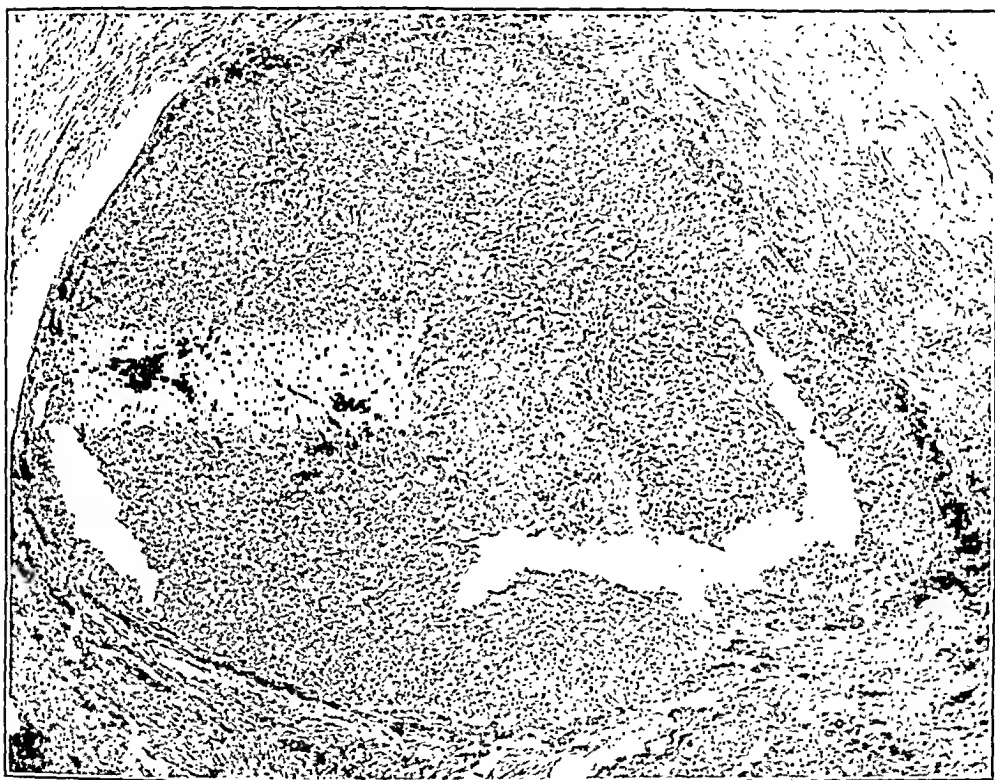


Fig. 1.—Granulosa cell tumor (mature homogeneous type). Note the periepithelial accumulation of lipoids (stained black) in the stroma simulating a thecalike reaction. (Sudan III hematoxylin-stained frozen section,  $\times 150$ .) (Reprinted from Greenblatt, R. B., Greenhill, J. P., and Brown, W. R.: *AM. J. OBST. & GYNEC.* 37: 929, 1939.)

In the human ovary, the stroma response is not as clear-cut. Certain patches of stroma may take on a hypertrophied and vacuolated appearance (Fig. 4), and the stroma cells in certain areas become more fusiform and full with larger nuclei but the transformation is not so marked as to arrest attention. An interstitial stroma cell response, in a measure comparable to that seen in the experimental animal, may be seen in the human ovary. This occurs in the stroma about the corpus atreticum. This is seen with regularity after gonadotropin medication. Enlargement of the corpora atretica occurs with new fibroblastic activity in the core of the body, and at the periphery there is a rejuvenation of the stroma which is merely a reawakening of dormant theca interna cells (Fig. 5), which had become incorporated into the basic substance of the ovary. These appear as a palisade of polyhedral cells that resemble the Leydig cell or the paralutein cell of the mature corpus

The luteinization of the theca interna occurs about the maturing follicle; after ovulation occurs the luteinization becomes increasingly abundant in the granulosa cells and further deposition of lipoids in the theca is arrested. If atresia of a somewhat maturing follicle occurs, then the hypertrophy and vacuolization of the theca becomes very pronounced. With impairment of the follicular apparatus by degeneration of the granulosa, compensatory theca cell hypertrophy seems to occur. Following gonadotropin medication theca cell luteinization about atretic or cystic unovulable follicles is the most constant and consistent stroma cell change (Fig. 6).

B. *The Follicular Apparatus.*—Most striking are the changes in the follicular apparatus of the ovary. Marked cystic dilatation of the follicles (distended with cloudy follicular fluid) lined by one or two seemingly compressed layers of granulosa cells showing chromatolysis and

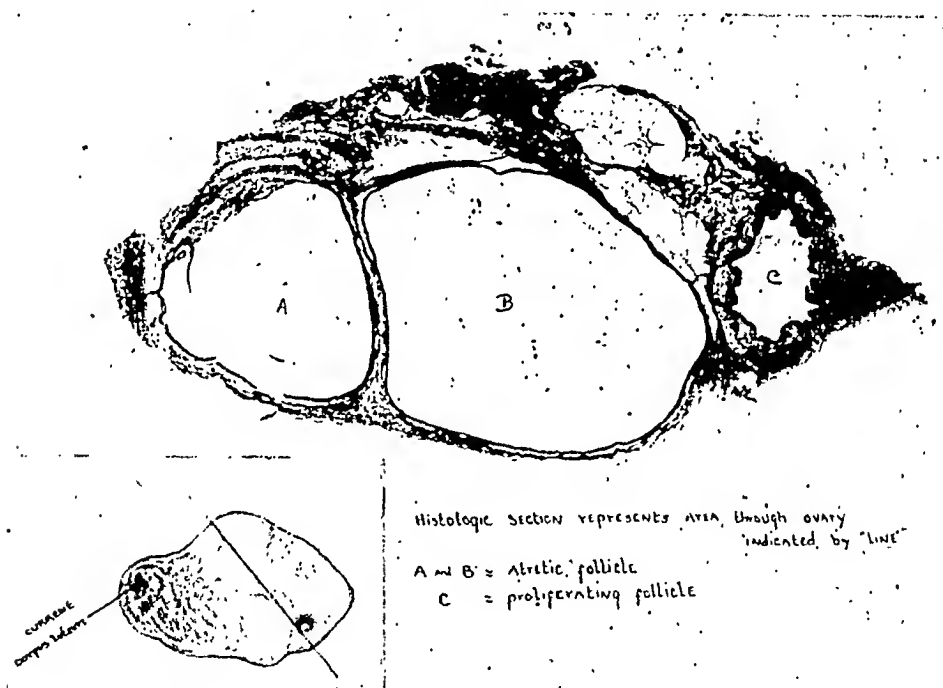


Fig. 7.—Note the atresia of the follicles at A and B. Proliferative follicle juxtaposed at C. Biopsy of human ovary following 90 units of pregnant mares' serum (gonadogen) administered intravenously; laparotomy fifteen hours later on sixteenth day of cycle. Note the current corpus luteum in gross drawing of the ovary.

pyknosis was the reaction most commonly present in all ovaries regardless of the type of gonadotropin medication, but most apparent after pregnant mares' serum (Fig. 7). Minimal to marked hypertrophy of the theca interna accompanied the follicular atresia. Frequently juxtaposed were follicles in various stages of maturation. Evidence of maturation of the follicle includes increase in size of the follicle, the wall lined by several layers of granulosa cells showing active proliferation as is evidenced by occasional mitotic figures, as well as signs of active secretion as is shown by the presence of Call-Exner bodies and the slight loosening of the granulosa by a coagulum giving the "streaming-out" phenomenon. The theca interna shows hypertrophy and some vacuolization of its cells as well as activity as is manifest by occasional mitoses. The perifollicular capillaries are congested (Fig. 8). Further progress in

luteum. There also appears to occur a luteinization of corpora fibrosa with increased lipoid deposition in that area. Aside from this, increased vascularity of the minute vessels in the stroma are apparent, not infrequently accompanied by extravasation of red blood cells in the vicinity of corpora fibrosa as well as in the core of corpora atretica.



FIG. 5.—Note the palisade of polyhedral cells about the corpus atreticum (*a*). The rejuvenated stroma cells were once active cells of the theca interna which have become incorporated into the basic substance of the ovary. Note the resemblance of the theca cells to the paralutein cells of the corpus luteum at (*b*). Biopsy from human ovary following a total of 90 units of pregnant mares' serum (Gonadogen administered on the third, fourth, and fifth days of the cycle; laparotomy on the seventh day of cycle.



FIG. 6.—Note the luteinization of the cells of the theca interna (Sudan III hematoxylin-stained frozen section). Note the lipoid deposition (photographs black) in the theca interna, eighth day of normal cycle following the administration of anterior pituitary extract (10 e.c. of gonadotropic factor).



maturation is marked by the pseudoluteinized appearance of the granulosa cells (contain but the minimal amount of lipoids), marked theca cell hypertrophy with lipoid storage, increased vascularity causing the jutting inwards of the theca giving the irregular infolding appearance



Fig. 10.—Note an apparently healthy ovum about to be washed out from the partially collapsed follicle on the ninth day of cycle following a course of equine gonadotropin. Note the dehiscence of the capsular part of the ovary, the rupture point, the basophilic coagulum, the ovum still situated in a recognizable cumulus, the decidua-like excrecence and the Call-Exner bodies in the granulosa cell layers.

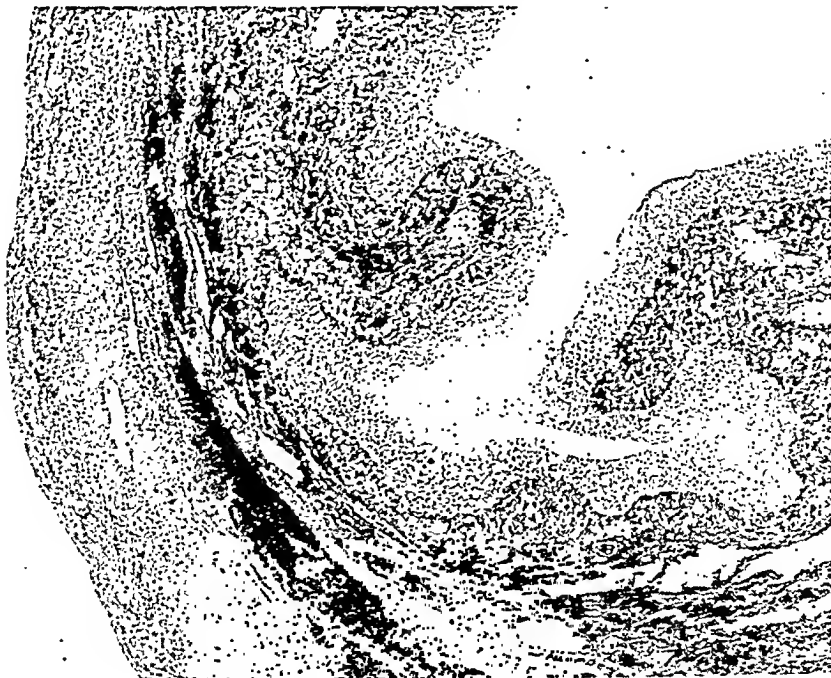


Fig. 11.—Marked congestion and perfollicular hemorrhage with disintegration of tissue following the administration of pregnant mares' serum (1,500 units of anteron). Note the pseudoluteinization of the piled-up granulosa cells and the hypertrophy of the cells of the theca interna.

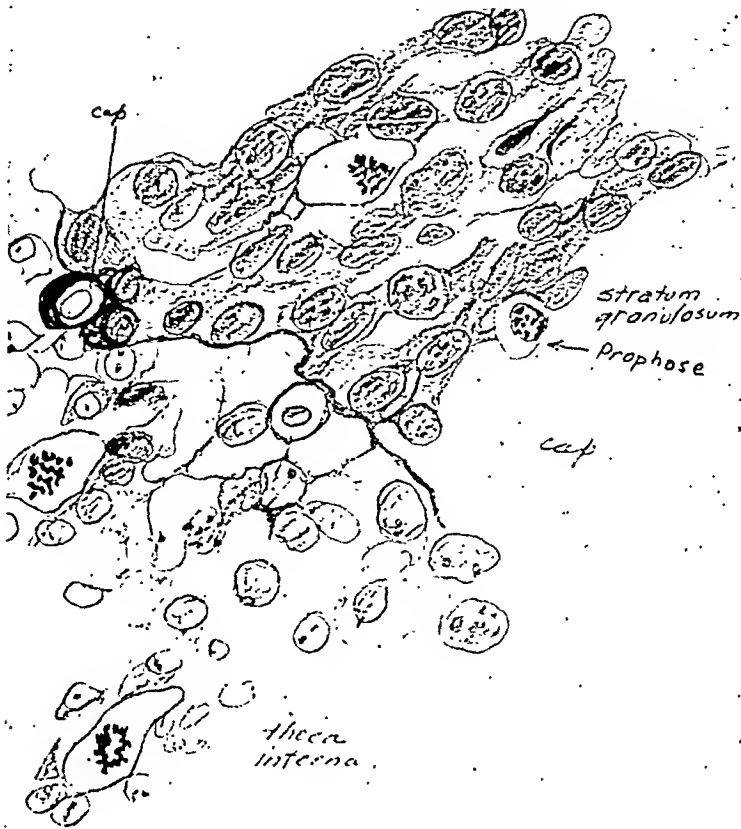


Fig. 8.—Camera lucida sketch  $\times 1700$  showing mitoses in stratum granulosum and theca interna. Biopsy of human ovary following intramuscular administration of 90 units of pregnant mares' serum (Gonadogen).

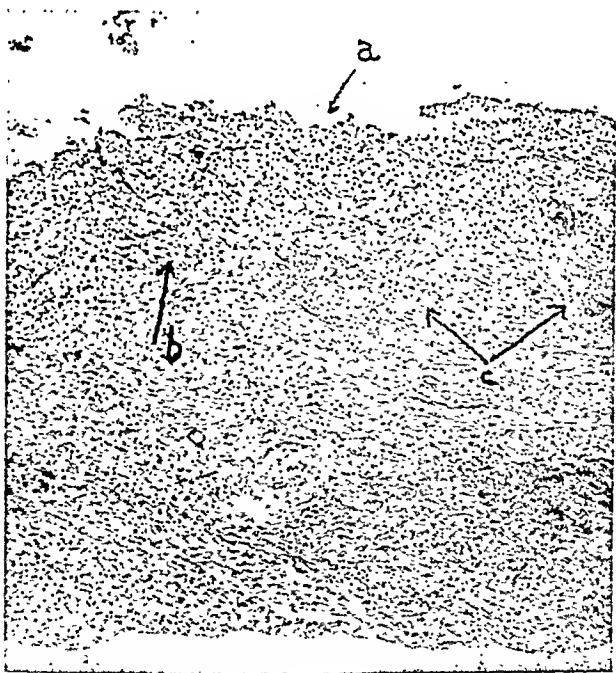


Fig. 9.—Note the pseudoluteinized granulosa cell layer (a), the hypertrophy of the cells of the theca interna (b), and the increased vascularity (c). Note the infolding of the membrana granulosa. Laparotomy performed on ninth day of regular cycle following administration of chorionic gonadotropin (Pranturon).

the Fallopian tube." We have been very fortunate in being able to demonstrate the process of actual rupture of the follicle in the human being. In this case it appears that rupture took place after the superficial wall, theca interna, theca externa, and surrounding stroma suffered disintegration by interstitial extravasation. Fig. 10 shows the dehiscence of the capsular part of the ovary, the partial collapse of the follicle and a normal ovum with its eumulus about to be expelled or washed out of the follicle. Note the Call-Exner bodies in granulosa cell layers of the follicle indicating active secretion. Note the mild hypertrophy of the theca interna. The only unusual or abnormal findings are the excessive extravasation of blood in the surrounding stroma and the tag of deciduallike tissue; both probably due to marked response to the pregnant mares' serum which was administered.<sup>12</sup>

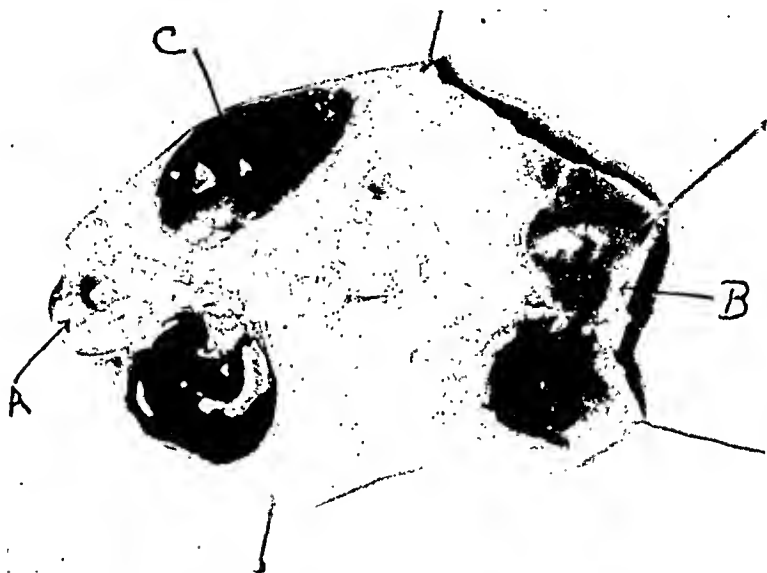


Fig. 14.—Bisected ovary showing A, the fully blossomed corpus luteum; B, fresh corpus luteum; and C, hemorrhagic lutein cyst, following the administration of chorionic gonadotropin with anterior pituitary synergist (10 c.c. of synapoidin) on twenty-first to twenty-third day of cycle, laparotomy on twenty-fourth day.

The orderly maturation of the follicles following the administration of gonadotropins is not frequently seen. Unpredictable is the response to a given dosage. Marked follicular stimulation, pseudoluteinization of piled up granulosa cell layers, hypertrophy of the cells of the theca interna, may be accompanied by a too vigorous response of the vascular bed component. The massive perifollicular hemorrhage and disruption of tissue is quite apparent in Fig. 11. Follicle atresia may occur because of early degeneration of the ovum (Fig. 12), disruption and desquamation of the hypertrophied granulosa cell layer. Thickening of the thecal wall with premature hyaline deposition may imprison a normal appearing ovum, thus forming the corpus atreticum (Fig. 13).

Complete shedding of the granulosa cell layer, accompanied by luteinization of the theca with hemorrhage into the cavity is not infrequently observed following gonadotropin stimulation. This is the hemorrhagic cyst which grossly may be mistaken for an hemorrhagic corpus luteum. Other forms of follicular atresia may occur due either to lack of liquor folliculi secretion or to its too rapid absorption leading to follic-

to the follicle (Fig. 9). Follicle rupture with the expulsion of the ovum probably occurs just prior to this phase, but the presence of infolding of the membrana granulosa does not necessarily signify rupture of the follicle. Davis and Koff said, "No one has actually seen a follicle (human) rupture nor observed its ovum prior to its transport into



Fig. 12.—Note the follicular atresia and the degeneration of the ovum while still surrounded by its cumulus. Note the paucity of the primordial follicles in the cortex. Biopsy from a sterile patient with functional amenorrhea following the administration of pregnant mares' serum (120 units of gonadogen) intramuscularly. No evidence of corpora albicantes or corpora lutea was present in the sections examined although one abortive corpus luteum was seen.

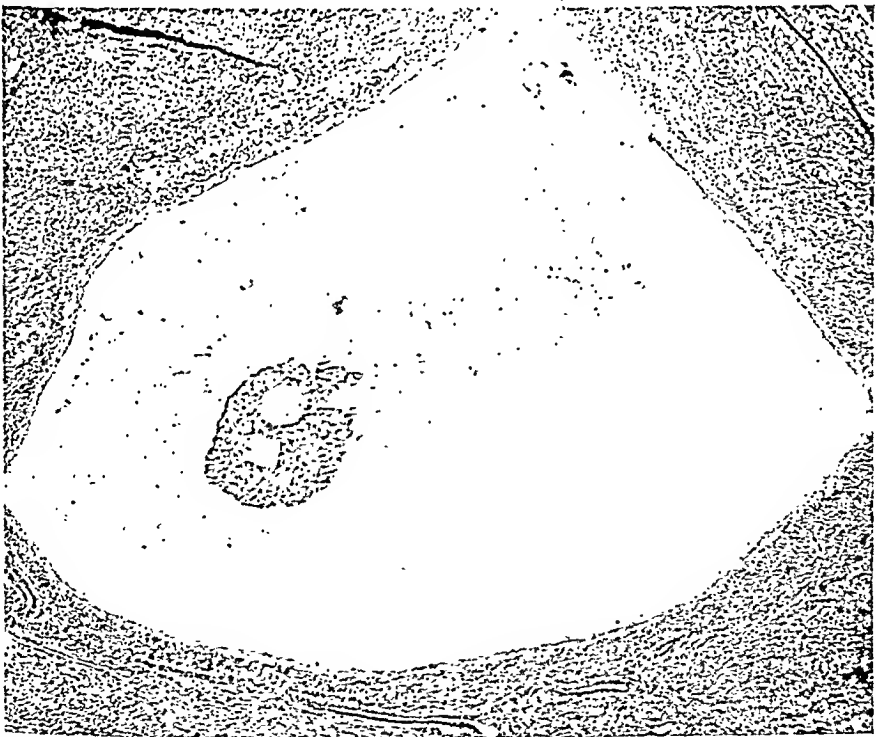


Fig. 13.—Early corpus atreticum. Premature hyaline deposition in the thecal wall immediately beneath the membrana granulosa is noted. The imprisoned ovum surrounded by its cumulus appears normal. Biopsy of ovary followed administration of gonadotropins.

Multiple corpora lutea in the same or in each of the ovaries have been observed though these are usually of the same age. Following gonadotropin medication there is frequently a rejuvenation of the degenerating cells of a previous corpus luteum. Accompanying this there is a vascular component response, i.e., fresh hemorrhage or extravasation of blood into the cavity of an older or degenerating corpus luteum (Fig. 16).

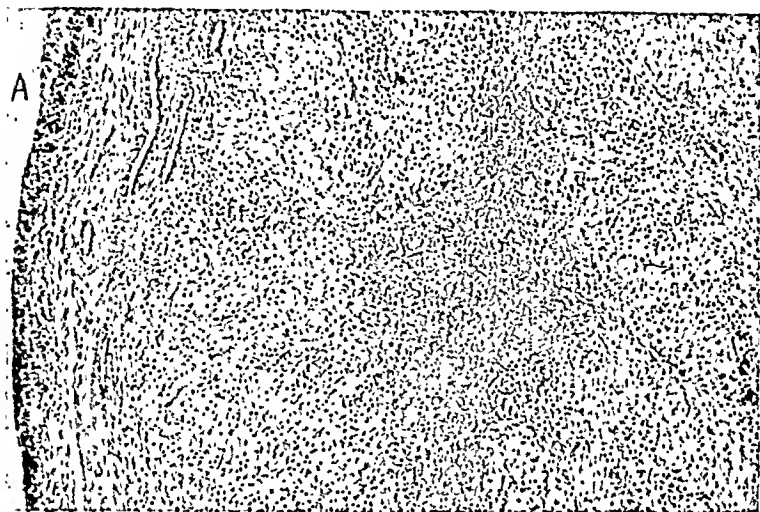


Fig. 16.—Biopsy of human ovary following pregnant mares' serum (90 units of gonadogen) intramuscularly, showing extravasation of blood into the cavity of the degenerating corpus luteum with seeming rejuvenation of the lutein cells. This corpus luteum was found deep in the cortex of the ovary. Above it at (A) is a large cystic follicle undergoing atresia.

#### DISCUSSION AND CONCLUSIONS

1. Thirty-six patients ranging from 15 to 49 years of age were subjected to laparotomy for various reasons, i.e., fibromyomas, legal sterilization, etc. Among these patients there was one who had delayed menarche (age 15), several with functional amenorrhea, and in one of these it was established that bleeding was anovulatory when it did occur. Gonadotropins were administered in varying doses for several days before laparotomy at a known time of the cycle. In several patients with ovarian dysfunction, such as functional amenorrhea, no evidence of past corpora lutea could be demonstrated in the biopsies nor was a progestinal response of the endometrium obtained following the course of gonadotropins. In the patients with normal cycles, superovulation was occasionally produced and in four instances recently ruptured follicles were discovered at laparotomy. It appeared that more or less similar degrees of stimulation of the ovary could be obtained with anterior pituitary extracts, equine gonadotropins, and also with chorionic gonadotropins if used in sufficient dosage (about 4,000 R.U.). Chorionic gonadotropin when combined with anterior pituitary synergist appeared to yield the most promising results, if the production of corpora lutea was taken as the goal. However, no matter what type or combination of gonadotropins was used, the most apparent histologic change was follicle atresia.

ular collapse. The occurrence of multiple corpora lutea (Fig. 14) in the same ovary following the administration of gonadotropins particularly if these are in different stages of development, may be accepted as an indication of superovulation (Fig. 15). The occurrence of a fresh corpus luteum along with a fully blossoming one is no absolute proof that the former is the result of the gonadotropic stimulant.



Fig. 15.—A, Histologic section through fully blossoming corpus luteum seen in Fig. 14 (A). Note the well developed fibroblastic wreath demarcating the central cavity and the mature paralutein cells growing down between the folds of lutein cells. B, Histologic section through the fresh corpus luteum seen in Fig. 14 (B). Note the ripening lutein granulosa cells and the hemorrhage into the central cavity.

## REFERENCES

- (1) Zondek, B., and Aschheim, S.: *Klin. Wchnschr.* 6: 248, 1927. (2) Smith, P. E., and Engle, E. T.: *Am. J. Anat.* 40: 159, 1927. (3) Engle, E. T.: *J. A. M. A.* 93: 276, 1929. (4) Geist, S. H.: *Am. J. Obst. & Gynec.* 26: 588, 1933. (5) Hamblen, E. C., and Ross, R. A.: *Endocrinology* 21: 722, 1937. (6) Davis, M. E., and Koff, A. K.: *Am. J. Obst. & Gynec.* 36: 183, 1938. (7) Siegler, S. L., and Fein, M. J.: *Ibid.* 38: 1021, 1939. (8) Greenblatt, R. B., and Torpin, R.: *J. M. A. Alabama* 9: 409, 1940. (9) Greenblatt, R. B., and Pund, E. R.: *South. M. J.* 34: 730, 1941. (10) Hartman, C. G.: *Bull. Johns Hopkins Hosp.* 63: 351, 1938. (11) Greenblatt, R. B., Greenhill, J. P., and Brown, W. R.: *Am. J. Obst. & Gynec.* 37: 929, 1939. (12) Greenblatt, R. B., and Krafka, J., Jr.: *Arch. Path.* 31: 634, 1941. (13) Robinson, M. R.: *Am. J. Obst. & Gynec.* 30: 18, 1935. (14) Schiller, Walter: Personal communication. (15) Clauberg, C.: *Zwanglose Abhandlungen aus dem Gebiete der Inneren Sekretion*, Leipzig, 1937, 2.

## THE SIGNIFICANCE OF FETAL ENVIRONMENTAL DIFFERENCES

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THE existence of a profusion of myths and superstitions has probably somewhat inhibited until modern times scientific thought and investigation into maternal-fetal relationships from the standpoint of how fetal development may be influenced by varying maternal factors. During the last twenty years, however, many facts and some very interesting hypotheses have accumulated in the literature of various fields—medicine, physiology, psychology, and biochemistry. The level of hormones in the mother's blood, the presence of drugs or toxins, the presence and level of certain food elements may all be thought of in the broader sense as constituent parts of the fetal environment. So also may such sounds or mechanical pressures as are perceptible to the fetus, and such maternal factors as emotional state, physical activity, fatigue, etc., which may alter in any way maternal blood levels of hormones, food elements, waste products, or oxygen.

Together such factors represent an environment as complete and probably fully as important as the social, physical, nutritional, and other components of the environments of infants or children. Since the period of intrauterine life is the period of actual formation of almost all adult structures, adverse environment during this time would undoubtedly occur more frequently and be of much greater eventual importance than at any other period were it not that the fetus is in certain ways protected by factors which tend to maintain at a near constant level, many environmental constituents. The homeostatic characteristics of the mother's body and its ability to maintain within narrow limits such blood constituents as chlorides, sugar, amino acids, calcium, phosphorus, iron, etc., eliminate many environmental extremes. The barrier offered by the placenta to certain substances protects against many infectious organisms and agents. The protection offered by maternal abdominal wall, uterus, and the amniotic fluid to mechanical and sound stimulation

2. Aside from the changes in the follicular apparatus, there occurred important changes in the other components of the ovary, i.e.:

- a. Marked theca cell hypertrophy with luteinization;
- b. Response of the vascular bed as seen in increased capillary congestion, extravasation of red blood cells into areas of loosened stroma and into the core of corpora atretica as well as in degenerating corpora lutea;
- c. Indistinct activation of patches of cells in the ovarian stroma;
- d. Rejuvenation of the dormant but once active theca cells that were incorporated into the basic substance of the ovary by forming a cellular wreath about the corpus atreticum. These reactivated cells take on a truly "interstitial cell" quality.

It is felt that the reactions in these component parts of the ovary are probably responsible for the occasional beneficial results seen following the use of gonadotropins in certain conditions as functional amenorrhea, oligomenorrhea, some types of dysmenorrhea, certain types of mastalgia and menometrorrhagia.

3. Since the prime interest in the employment of gonadotropins is an attempt to rectify ovarian dysfunction which manifests itself as functional menorrhagia or functional amenorrhea or sterility, the impression has gained currency that these disturbed entities are functional rather than organic. It must be stressed that structure and function are indissolubly linked to each other. The concept of functional disturbance without organic disturbance must be relegated to the scrap heap of obsolete theories.<sup>13</sup> In the evaluation of the histologic changes in the human ovary following the administration of gonadotropins, it must be borne in mind that more or less similar changes are seen in the ovary in some types of dyspituitarism (as in idiopathic hirsutism, certain types of menorrhagia and secondary amenorrhea): in hyperprolancemia (as in hydatid mole or chorionepithelioma); in pregnancy and pubescence;<sup>14</sup> in fetal ovary under the influence of pregnancy.<sup>15</sup>

4. It is evident, however, that orderly follicle maturation and ovulation and corpus luteum formation in patients with ovarian dysfunction was not attained. It is hoped that proper dosage, time interval and combination of gonadotropins may yet yield more desirable results, so that it may be used in the anovulatory sterile woman.

The author gratefully acknowledges the source of the gonadotropins used in this study which were generously supplied by the following pharmaceutical organizations: Extract of the anterior pituitary as gonadotropic factor by Armour and Co.; equine gonadotropin as gonadogen by the Upjohn Co.; chorionic gonadotropin as pranturon by Schering Corporation; combined chorionic gonadotropin with anterior pituitary synergist as synapoidin by Parke, Davis and Co. Other gonadotropins such as gonadin (Cutter), anteron (Schering), and prephysin (Chappel) were also used. The stilbestrol, as synestrol, was supplied by Sharpe and Dohme.

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